Clinical evaluation of a formulation containing *Curcuma longa* and *Boswellia serrata* extracts in the management of knee osteoarthritis

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Abstract. A formulation containing *Curcuma longa* and *Boswellia serrata* extracts (CB formulation) was evaluated for safety and efficacy in osteoarthritic patients and directly compared with the selective COX-2 inhibitor, celecoxib. In total, 54 subjects were screened, 30 subjects were enrolled and 28 completed the study. The treatment was well tolerated and did not produce any adverse effect in patients, as judged by the vital signs, hemogram, liver and renal function tests. The CB formulation at 500 mg administered twice a day, was more successful than administering celecoxib 100 mg twice a day for symptom scoring and clinical examination. The formulation was found to be safe and no dose-related toxicity was found.

Introduction

Osteoarthritis (OA) is a degenerative joint disease that is a leading cause of physical disability and impaired quality of life in industrialized nations. The exact etiology of OA is not fully understood. Although age is the strongest predictor of the development of OA, obesity, trauma and physically demanding occupations also increase the risk of OA of the hand, knee and hip. OA imposes a considerable functional burden on affected individuals. NHANES III (the Third National Health and Nutrition Examination Survey) revealed that >8% of adults in the USA have symptomatic OA (1). A French study found that >80% of clinical OA patients reported limitations in their daily lives, including basic tasks, work and leisure activities, and these limitations impacted the quality of life of affected patients, often leading to depression and social isolation (2). OA imposes a significant economic burden on patients and healthcare systems (3-6).

Despite the increasing number of patients with OA, treatments to manage the condition remain symptomatic, designed to control pain and improve function and quality of life while attempting to limit the adverse events associated with the medication. Guidelines for the management of OA have been published by the Osteoarthritis Research Society International (OARSI) (7,8) and the European League Against Rheumatism (EULAR) (9-11). These guidelines indicate that a combination of pharmacological and non-pharmacological modalities is the most effective strategy for managing the pain and disabilities associated with OA. Acetaminophen is recommended as the first line therapy and a switch to non steroidal anti-inflammatory drugs (NSAIDs) is recommended if acetaminophen does not adequately control symptoms or if there are signs of clinical inflammation. Acetaminophen, however, is considerably less efficient than NSAIDs in providing symptomatic relief (12,13), and patients are, sooner or later, forced to switch to NSAIDs. The long-term use of NSAIDs is associated with gastrointestinal, renal and cardiovascular risks. Given the efficacy, safety and tolerability issues associated with NSAIDs, the development of new agents to manage OA without adverse events remains a priority.

Traditional medicines using plant-derived compounds offer a safer alternative tool for the management of many chronic ailments. One such formulation is evaluated in this study as a treatment option for OA of the knee. A combination of the common spice *Curcuma longa* and the active principles of *Boswellia serrata* (CB formulation) was tested in OA patients and the efficacy and safety were evaluated in direct comparison with a selective cyclooxygenase-2 inhibitor, celecoxib. Boswellia gum resin and turmeric have been in active use in traditional medicine for thousands of years. Boswellia extract has shown promise for the treatment of asthma (14), rheumatoid arthritis (15), Crohn's disease (16), OA of the knee (17-19) and collagenous colitis (20). The biological activity of *Boswellia serrata* arises from the boswellic acids, of which the 3-O-acetyl-11-keto-boswellic acid (AKBA) is the most active (21-24). AKBA is an inhibitor of the lipoxygenase pathway of arachidonate metabolism and possesses significant anti-inflammatory and anticancer properties. The AKBA

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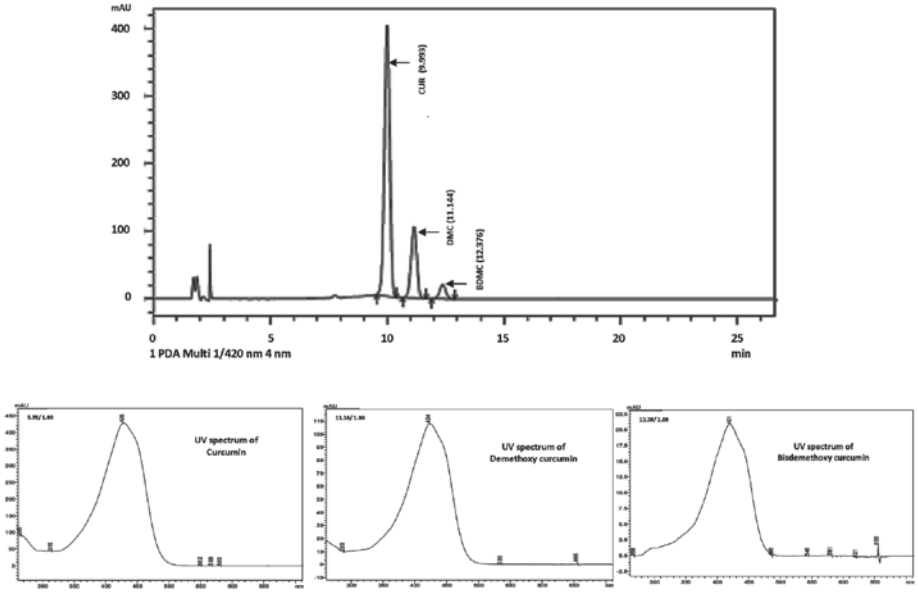

Figure 1. HPLC chromatogram and UV spectra of curcuminoids in *Curcuma longa* extract.

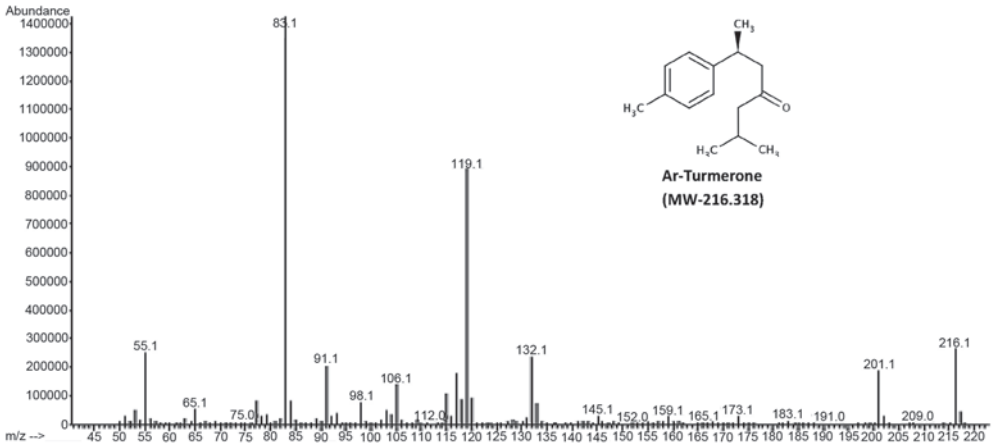

Figure 2. Gas chromatography mass spectrum of ar-Turmerone (MW-216.318).

content of commercial boswellia extracts is low at ~2% and a preparation with enhanced AKBA content (10% AKBA) was used in this study. The oral bioavailability of curcumin is poor (25), so the wide range of physiological activities of curcumin have not yet been translated into clinical benefits. A formulation of curcumin with enhanced bioavailability was the other component of the study drug. Curcumin, the active component of turmeric, possesses antioxidative, anti-inflammatory and anticancer properties and may modulate a large number of signaling pathways and thus possesses an extremely wide range of biological activities. Glycosaminoglycan synthesis is required for cartilage repair. Boswellia prevents a decrease in glycosaminoglycan levels, whereas NSAIDs may disrupt glycosaminoglycan synthesis, which, in turn, may accelerate cartilage damage. The non-acid section of the gum has pain-relieving qualities (26).

The curcuminoids were analyzed with an HPLC system which used a 60/40 water THF mobile phase, C18 column and the chromatogram was monitored at 420 nm. The assay analysis was performed by using the USP reference standards of individual curcuminoids (CAS numbers: 458-37-7, 24939-17-1 and 24939-16-0). The retention times of various peaks in the sample were parallel to those of the curcuminoid standards and the sample purity was determined by comparing the peak areas of individual peaks present in the standard vs. the sample. The HPLC chromatogram and UV spectra of curcuminoids in the *Curcuma longa* extract are shown in Fig. 1. The retention times for the peaks from the three curcuminoids (curcumin, demethoxycurcumin and bis-demethoxycurcumin) in the reference standard and sample were identical (9.993, 11.144 and 12.376 min, respectively).

The major component of turmeric essential oils, ar-Turmerone was characterized using GC-MS. With a molecular mass of 216.318, ar-Turmerone is confirmed on the mass spectrum in Fig 2.

AKBA, was quantified by the HPLC system using an acetonitrile:water (90:10) mobile phase and the chromatogram was monitored at 254 nm. The AKBA peak was eluted at a retention time of 8.9 min and has characteristic UV spectra (Fig. 3). The assay quantification was performed using a

Table I. Treatment schedule.

Visit no.	Tasks accomplished
1	Informed consent obtained, medical history and general examination
	Joint examination
	X-ray examination
	Hemogram (TC, DC, ESR)
	Liver function tests (serum bilirubin, SGOT, SGPT, SAP)
	Renal function tests (blood urea, serum creatinine)
	Other tests (ASO, CRP, RF, blood sugar)
	Enrolled/rejected as per inclusion/exclusion criteria
2	Pre-examinations on screened patients
	Assignment to one of the treatment groups as per randomization
	T0 baseline characteristics:
	Vital signs
	Knee AP view and lateral view (X-ray)
	Hemogram
	Liver function test
	Renal function test
	Symptom score (joint pain, walking distance)
	Patients were given a diary and trained in documentation
	Treatment supplies provided for two weeks and documented
	Discharge instructions regarding next visit
3-7	Follow-up for all subjects:
	Vital signs
	Symptom score
	Clinical examination
	Treatment supplies provided for two weeks and documented
	Discharge instructions regarding next visit
8	Follow-up for all subjects:
	Vital signs
	Symptom score
	Clinical examination
	Patient diary was collected and documented
	Final discharge instructions

TC, total count of white blood cells; DC, differential white blood cell count; ESR, erythrocyte sedimentation rate; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SAP, serum alkaline phosphatase; ASO, anti-streptolysin O; CRP, C-reactive protein; RF, renal function; AP, anterior-posterior.

reference standard (Sigma Aldrich CAS no.: 67416-61-9) and revealed 10% AKBA, a representative chromatogram is shown in Fig. 3.

The purpose of this study was to evaluate the efficacy, safety and tolerability of CB formulation compared with celecoxib for the management of knee OA.

Table II. Comparison of baseline demographic and other characteristics between treatment groups.

Demographic characteristic	Group I (n=14) mean ± SD	Group II (n=14) mean ± SD
Age (years)	49.70±8.20	47.20±9.70
Males	6	6
Females	8	8
Temperature (˚C)	37.00±0.00	37.00±0.00
Height (cm)	154.30±9.20	158.70±7.50
Weight (kg)	59.60±11.30	65.92±13.45
BMI (kg/cm^2)	25.00±3.50	26.09±3.94
BP-systolic (mmHg)	121.40±11.0	129.28±14.91
BP-diastolic (mmHg)	79.29±8.29	80.71±8.28
Pulse rate (per min)	78.43±5.02	78.14±6.29
Respiration (per min)	22.29±1.54	21.21±1.25

BP, blood pressure.

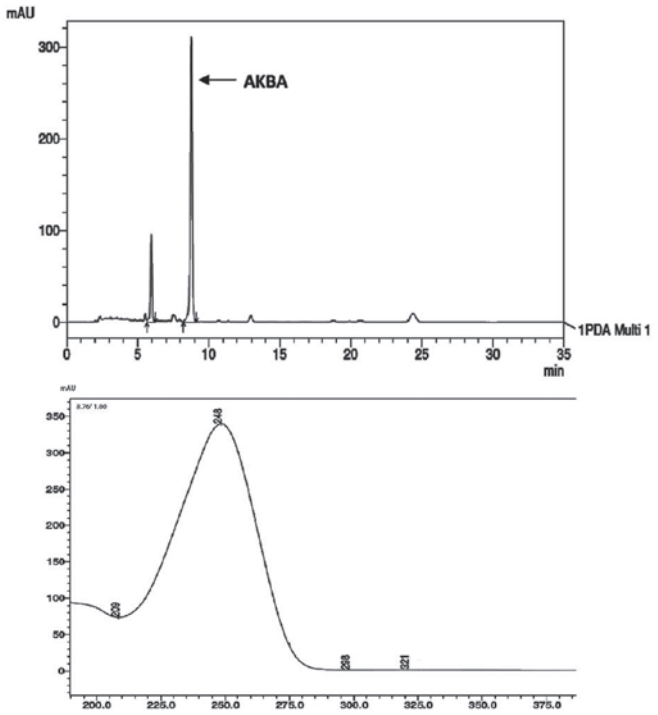

Figure 3. HPLC chromatogram of *Boswellia serrata* extract showing peak and UV spectra of AKBA. AKBA, 3-O-acetyl-11-keto-boswellic acid.

Materials and methods

Study design. The CB formulation consisted of 350 mg *Curcuma longa* extract (BCM 95®, Arjuna Natural Extracts Ltd, Aluva, Kerala, India) containing 70% curcumin, 17% demethoxycurcumin, 3.5% bis-demethoxycurcumin and 7.5% turmeric essential oils and 150 mg *Boswellia serrata* extract (BosPure®, Arjuna Natural Extracts Ltd, Aluva, Kerala, India) containing 75% boswellic acids and 10% AKBA in 500-mg hard gelatin capsules. The study was performed at the Anugraha Medical Centre, Kochi, India as a two arm clinical

Table III. Analysis of joint pain measurements.

		Group I		Group II	
Time points	Response	No.	%	No.	%
T0	No	0	0.00	0	0.00
	Mild	2	14.29	3	21.43
	Moderate	11	78.57	10	71.43
	Severe	1	7.14	1	7.14
T2	No	1	7.14	1	7.14
	Mild	2	14.29	3	21.43
	Moderate	10	71.43	10	71.43
	Severe	1	7.14	0	0.00
T4	No	1	7.14	1	7.14
	Mild	4	28.57	3	21.43
	Moderate	9	64.29	10	71.43
	Severe	0	0.00	0	0.00
T6	No	1	7.14	0	0.00
	Mild	5	35.71	3	21.43
	Moderate	8	57.14	11	78.57
	Severe	0	0.00	0	0.00
T8	No	1	7.14	0	0.00
	Mild	7	50.00	4	28.57
	Moderate	5	42.86	10	71.43
	Severe	0	0.00	0	0.00
T10	No	2	14.29	1	7.14
	Mild	8	57.14	5	35.71
	Moderate	4	28.57	8	57.14
	Severe	0	0.00	0	0.00
T12	No	2	14.29	1	7.14
	Mild	9	64.29	6	42.86
	Moderate	3	21.43	8	50.00
	Severe	0	0.00	0	0.00

There is a statistically significant difference between joint pain at the baseline compared with pain at the end of the study within the groups ($P<0.05$). At the start of the study, 11 subjects in Group I and 10 subjects in Group II presented with a 'moderate' joint pain. Following treatment with CB formulation for three months, only three patients were classified as having a 'moderate' joint pain in Group I, while eight subjects in Group II had 'moderate' joint pain status even following treatment with celecoxib. CB, a formulation containing *Curcuma longa* and *Boswellia serrata* extracts.

Table IV. Analysis of walking distance measurements.

		Group I		Group II	
Time points	Distance (m)	No.	%	No.	%
T0	<100	1	7.14	1	7.14
	100-500	5	35.71	3	21.43
	500-1000	5	35.71	6	42.86
	>1000	3	21.43	4	28.57
T2	<100	0	0.00	0	0.00
	100-500	2	14.29	1	7.14
	500-1000	8	57.14	9	64.29
	>1000	4	28.57	4	28.57
T4	<100	0	0.00	0	0.00
	100-500	1	7.14	1	7.14
	500-1000	3	21.43	2	14.29
	>1000	10	71.43	11	78.57
T6	<100	0	0.00	0	0.00
	100-500	1	7.14	1	7.14
	500-1000	2	14.29	3	21.43
	>1000	11	78.57	10	71.43
T8	<100	0	0.00	0	0.00
	100-500	1	7.14	0	0.00
	500-1000	1	7.14	3	21.43
	>1000	12	85.71	11	78.57
T10	<100	0	0.00	0	0.00
	100-500	0	0.00	0	0.00
	500-1000	2	14.29	2	14.29
	>1000	12	85.71	12	85.71
T12	<100	0	0.00	0	0.00
	100-500	0	0.00	0	0.00
	500-1000	1	7.14	2	14.29
	>1000	13	92.86	12	85.71

There is statistically significant difference between joint pain at baseline compared with pain at the end of the study within the groups ($P<0.05$). However, between the groups there is no statistically significant difference ($P>0.05$).

trial with a positive control and was conducted with 30 osteoarthritic patients divided into two groups of 15 subjects. Each patient voluntarily enrolled in the study and received treatment for 12 weeks. The two groups received the following treatment: Group I, oral administration of CB formulation 500 mg capsule (twice daily). Group II, oral administration of celecoxib 100 mg capsule (twice daily).

Subjects were enrolled on a first-come-first-served basis and assigned a subject number sequentially. The assignment of each subject to the treatment group was determined randomly. All subjects visited the clinic at least eight times. At each visit, the vital signs, symptom scoring and clinical examination results were recorded. Liver and renal function tests were performed at the beginning (T0), after 6 weeks (T6) and at the end of study (T12) in order to assess the safety of the study drug. All study volunteers provided written informed consent to participate and the study was approved by the Independent Ethics Committee of Anugraha Medical Centre, Kakkanad, Kochi, Kerala, India. Table I details the schedule of visits and the procedures adopted at each visit.

Patient population. Patients of both genders, aged between 18 and 65 years, who were medically stable with a moderate form of OA, evidenced by the narrowing of the medial joint space with swelling, were recruited for this study. Long standing OA with a gross deformity, patients with a severe form of OA evidenced by gross radiological findings, swelling

Table V. Analysis of joint line tenderness.

		Group I		Group II	
Time points	Response	No.	%	No.	%
T0	No	2	14.29	3	21.43
	Mild	0	0.00	0	0.00
	Moderate	12	85.71	11	78.57
	Severe	0	0.00	0	0.00
T2	No	4	28.57	3	21.43
	Mild	1	7.14	2	14.29
	Moderate	9	64.29	9	64.29
	Severe	0	0.00	0	0.00
T4	No	5	35.71	4	28.57
	Mild	2	14.29	2	14.29
	Moderate	7	50.00	8	57.14
	Severe	0	0.00	0	0.00
T6	No	6	42.86	4	28.57
	Mild	3	21.43	4	28.57
	Moderate	4	35.71	6	42.86
	Severe	0	0.00	0	0.00
T8	No	6	42.86	5	35.71
	Mild	4	28.57	4	28.57
	Moderate	3	28.57	5	35.71
	Severe	0	0.00	0	0.00
T10	No	7	50.00	6	42.86
	Mild	3	28.57	4	28.57
	Moderate	3	21.43	4	28.57
	Severe	0	0.00	0	0.00
T12	No	8	57.14	6	42.86
	Mild	3	35.71	5	35.71
	Moderate	1	7.14	3	21.43
	Severe	0	0.00	0	0.00

There is a statistically significant difference between joint pain at baseline compared with pain at the end of the study within the groups ($P<0.05$). At the start of the study, 12 subjects in Group I and 11 subjects in Group II were classed as exhibiting a 'moderate' joint line tenderness. Following treatment with a CB formulation for three months, only one patient was classed as exhibiting a 'moderate' level of the joint line tenderness in Group I, while three subjects in Group II had 'moderate' joint line tenderness even following treatment with celecoxib. Between the groups, there is no statistically significant difference ($P>0.05$). CB, a formulation containing *Curcuma longa* and *Boswellia serrata* extracts.

Table VI. Analysis of crepitus at various time points.

		Group I		Group II	
Time points	Response	No.	%	No.	%
T0	No	1	7.14	2	14.29
	Mild	6	42.86	5	35.71
	Moderate	7	50.00	6	42.86
	Severe	0	0.00	1	7.14
T2	No	2	14.29	2	14.29
	Mild	6	42.86	6	42.86
	Moderate	6	42.86	5	35.71
	Severe	0	0.00	1	7.14
T4	No	2	14.29	2	14.29
	Mild	7	50.00	7	50.00
	Moderate	5	35.71	4	28.57
	Severe	0	0.00	1	7.14
T6	No	2	14.29	2	14.29
	Mild	7	50.00	9	64.29
	Moderate	5	35.71	3	21.43
	Severe	0	0.00	0	0.00
T8	No	4	28.57	3	21.43
	Mild	5	35.71	9	64.29
	Moderate	5	35.71	2	14.29
	Severe	0	0.00	0	0.00
T10	No	4	28.57	3	21.43
	Mild	7	50.00	10	71.43
	Moderate	3	21.43	1	7.14
	Severe	0	0.00	0	0.00
T12	No	5	35.71	4	28.57
	Mild	9	64.29	10	71.43
	Moderate	0	0.00	0	0.00
	Severe	0	0.00	0	0.00

There is a statistically significant difference between joint pain at baseline compared with pain at the end of the study within the groups ($P<0.05$). At the start of the study, 50% of patients in the groups were classed as having a 'moderate/severe' crepitus, but at the end of the study all patients were in the 'no/mild' crepitus category. However, between the groups there is no statistically significant difference ($P>0.05$).

and restricted mobility, nursing mothers, patients with a history of rheumatoid or reactive arthritis, or clinical findings of significant systemic disease, drug or alcohol abuse, malnutrition or any condition which in the opinion of the Principal Investigator would place the subject at risk or affect the conduct of the study or interpretation of the results, were excluded from this study.

In total, 54 subjects were screened, 30 were enrolled and 28 subjects completed the study. Each enrolled subject was assigned a number on a first-come-first-served basis and assigned to a treatment group randomly.

The following criteria were used to withdraw a subject from the study: i) any indication of an allergic reaction to the treatment; ii) the patient developed severe symptoms that were uncontrollable with the study drugs; iii) withdrawal of consent; iv) administrative reasons, such as patient non-compliance or major protocol violation (pregnancy or alcohol consumption during the study) and v) any condition that might put the subject at undue risk. Two patients decided to not participate further during the course of the study: one patient from the CB formulation group withdrew from the study due to personal reasons and one patient from the celecoxib group withdrew from the study due to the inadequate control of symptoms.

There were no statistically significant differences in age, height, weight, BMI, temperature, BP-systolic, BP-diastolic, pulse rate and respiration between the subjects in the two groups.

Efficacy assessment. The efficacy of the CB formulation over the treatment period was evaluated by symptom scoring and clinical examination.

Symptom scoring was performed by an orthopedician evaluating the subjects for joint pain (measured as 'no', 'mild', 'moderate' or 'severe') and walking distance (recorded as, >1000, 500-1000, 100-500 or <100 m) and the responses were documented. Clinical examination of the joints was performed for the following parameters: i) joint tenderness, measured either as 'no', 'improved', 'same' or 'worsened'; ii) crepitus, measured either as 'no', 'mild', 'moderate' or 'severe'; iii) swelling, measured in centimeters using a measuring tape, bilaterally; iv) range of movements, measured in degrees using a goniometer, bilaterally; v) thigh measurements, measured using measuring tape around the thigh at a distance 5 cm from the upper border of the patella and recorded in centimeters; vi) warmth measured as 'yes' or 'no' and vii) gait, assessed as 'normal' or 'abnormal'.

Safety assessment. The safety of the CB formulation over the treatment period was evaluated by measuring; i) vital signs; ii) hemogram measurements including, total white blood cell count (TC), differential white blood cell count as polymorphonuclear neutrophils (DC-P), lymphocytes (DC-L), eosinophils (DC-E) and erythrocyte sedimentation rate (ESR); iii) Liver function test (LFT), including serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase (SAP) and iv) renal function tests (RFT), including blood urea and serum creatinine. Vital signs were measured at each visit and a hemogram, LFT and RFT were measured prior to treatment, following 6 weeks of treatment and at the end of the treatment period (12 weeks).

Statistical analysis. Statistical analysis of the data was performed using one-way ANOVA to analyze safety and efficacy data in order to determine the statistically significant differences between treatment groups or between time points within the groups. The test was used to analyze data on joint pain measurements, walking distance measurements, joint line tenderness, crepitus, range of movements and swelling of the joints. $P<0.05$ was considered to indicate a statistically significant difference.

Results and discussion

The baseline characteristics of the two treatment groups are provided in Table II. There were no statistically significant differences between the two groups. Demographic characteristics of the groups were comparable.

The efficacy of CB formulation compared with that of celecoxib for the management of the symptoms of OA was evaluated by symptom scoring and clinical examination, and analyzing the data as a function of time for the two treated groups. The CB formulation was evaluated at a dose of 500 mg capsules twice daily and the celecoxib capsule was administered at a dose of 100 mg twice daily. Symptom refers to the complaints expressed by the patient and scored depending on severity. The data were analyzed statistically.

Table VII. Analysis of range of movement of knees.

	Group I		Group II	
Time points	Left knee	Right knee	Left knee	Right knee
T0	128.2	126.4	125.4	125.4
T2	130.4	131.4	126.1	126.1
T4	131.1	131.0	131.1	130.7
T6	131.9	132.1	129.6	129.6
T8	132.4	132.4	132.5	132.5
T10	133.1	133.2	132.1	131.8
T12	133.9	133.2	133.2	133.2

There is a statistically significant difference between the range of movements in the right and left knees at the baseline compared with at the end of the study within the groups ($P<0.05$). The differences in the range of movements of the knees were comparable in the groups and there was no significant change between the two groups.

OA joint pain is a deep pain localized to the joint and is measured by querying the patient and scoring it as no/mild/moderate/severe during each visit. The results of this analysis for the two treatment groups are presented in Table III. There was a significant improvement in pain scores within Groups I and II over a period of 12 weeks, but there was no significant difference between the groups. At the baseline, 85.71% of the subjects were in the moderate/severe category in Group I and 78.57% in Group II. At the end of the study, only 21.43% of subjects in Group I were in the moderate/severe category whereas 50% of Group II remained in the moderate/severe category.

Walking distance refers to the maximum distance a person is capable of walking without any limiting pain. The walking distance measurements were recorded at each visit and are provided in Table IV. Statistically significant improvements in the proportion of individuals scoring a walking distance of >1000 m were observed within the two groups over a period of 12 weeks. In Group I, 92.86% of subjects could walk >1000 m compared with 85.71% in Group II following treatment. Between the two groups, there were no significant changes.

Joint line tenderness was elicited by palpating along the joint line and was measured by querying the patient and recording the response as no/mild/moderate/severe and was recorded at each visit, the results of which are presented in Table V. Significant improvements were observed in the two groups. The percentage of patients in the moderate/severe category decreased from 85.71 to 7.14% in Group I over the 12 week period, whereas in Group II a decrease from 78.57 to 21.43% was observed. This showed that 92.85% of the patients in Group I demonstrated an improvement or had no joint line tenderness compared with 78.57% in Group II.

Crepitus (a crackling or grating feeling or sound in the joints) is elicited by palpating the joint on movement and

scoring it as no/mild/moderate/severe. These were recorded at each visit and are presented in Table VI. The range of movement of the knee is measured for flexion/extension movement and the normal range is from 0-135˚ (0 being a neutral position and the increasing flexion of the joint is normally up to 135˚). It is measured using a goniometer and is measured by asking the patient to flex the joint to the greatest possible extent and the maximum value was recorded. Results for the left and right knee are recorded in Table VII. A significant improvement in crepitus and the range of movement were seen within both groups. The other parameters studied, namely, joint swelling, warmth of joint, gait and thigh measurements were unaffected by any of the drugs or combination tested.

The safety of the CB formulation was evaluated by measuring vital signs (systolic and diastolic BP, pulse rate, respiratory rate), hemogram measurement (TC, DC-P, DC-L, DC-E, ESR), LFTs (SGOT, SGPT, SAP, bilirubin), RFTs (blood urea, serum creatinine). None of these parameters were adversely modified by CB formulation. There were also no adverse events reported in the study.

In conclusion, the CB formulation 500 mg, administered twice daily demonstrated a greater improvement in the treatment of OA than celecoxib 100 mg twice daily in the scores for pain, walking distance and joint line tenderness. The CB formulation was equally as effective as celecoxib in alleviating crepitus, and increasing the range of joint movements. The CB formulation was well tolerated and no dose-related toxicity was found. The efficacy and tolerability of CB formulation used in the current study was shown to be superior to those of celecoxib (NSAID) for treating active OA.

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