International Journal of Basic & Clinical Pharmacology
Rajendran K et al. Int J Basic Clin Pharmacol. 2021 Jan;10(1):1-9
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20205406

Original Research Article

Assessment of safety and efficacy of Karallief® Easy Climb™, an herbal extract blend for supporting joint health: a double-blind, placebo-controlled, randomized clinical trial

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Received: 10 November 2020
Revised: 24 November 2020
Accepted: 25 November 2020

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ABSTRACT

Background: Osteoarthritis is common among the aging population worldwide. The current techniques to manage osteoarthritis focus on relieving pain and slowing the progression of the disease. Herbal or natural supplements have shown promise in achieving both these treatment goals. Two new proprietary herbal extract blends, Karallief® Easy Climb™ (KEC) and herbal extracts with glucosamine (HEG), are combinations of several natural products shown to be effective in the treatment of knee osteoarthritis. The current study tested the efficacy and safety of KEC and HEG versus a placebo control.
Methods: This is a randomized, double-blind and placebo-controlled study. A total of 120 patients were divided into 3 groups and were given KEC, HEG and Placebo in the ratio 1:1:1. Treatment results were assessed using the 30 second chair stand test, WOMAC test, knee flexion test and joint space measurement using X-rays of the knee joint.
Results: The study found that the herbal supplements HEG and KEC significantly reduced osteoarthritis-related knee pain and increased joint mobility and were safe to use during 120 days of treatment. Both supplements resulted in an improvement in the 30 second chair stand test results, WOMAC pain scores, knee flexion, and joint space width as measured by X-ray, as compared to the placebo.
Conclusions: Natural supplements such as HEG and KEC improve knee osteoarthritis symptoms and can be a safe and effective treatment option for patients with osteoarthritis.

Keywords: Knee osteoarthritis, Herbal supplement, Natural treatment, Randomized clinical trial, Joint health, Joint mobility

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis affecting around 250 million people globally and is one of the leading causes of disability which affects the joints.[1] Prevalence of knee osteoarthritis is about 22 to 39% in India and an estimated 32.5 million Americans are affected by it each year.[2,3]

OA is a chronic, progressive musculoskeletal disorder involving movable joints characterized by gradual loss of cartilage due to cell stress and by extracellular matrix degradation initiated by micro-and macro-injury which results in bones rubbing together and creating pain, stiffness, crepitus and impaired movement.[4,5] It also results from joint deterioration connected to aging.[6]

Pain is the main symptom of OA and typically transitions from intermittent weight-bearing pain to a more persistent, chronic pain where nociceptive and neuropathic mechanisms are involved at both local and central levels.[1]

The primary goal of OA treatment is to reduce symptoms and slow the progression of the disease. Some patients have knee or hip replacements if pain becomes unmanageable with medication.[7] Treatments that can manage pain and improve symptoms, functionality, and quality of life are highly sought after.

Current OA management techniques include exercise, clinical devices, weight management or pharmacologic approaches such as topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen.[8,9] When patients have severe pain that is not manageable with Over the counter (OTC) pain medications, opioids may be prescribed.[7] Corticosteroid injections may also be used to reduce inflammation and improve knee mobility.[9]

Many patients experiencing OA are elderly and have comorbidities such as cardiovascular and kidney diseases that may make it dangerous for them to take pain medications, such as NSAIDs, for an extended period of time.[10,11] NSAIDs also pose a risk for serious gastrointestinal side effects including ulceration and bleeding.[12]

Alternative approaches to improve symptoms and reduce pain have been explored as options for the treatment of osteoarthritis.[13,14] This study was conducted to test the efficacy and safety of two such proprietary herbal extract blends, KEC and HEG, in improving the symptoms of knee osteoarthritis as compared to a placebo control.

METHODS

This is a randomized, 120 days, double-blind, placebo-controlled study. The reporting of the study has been done according to CONSORT (consolidated reporting of randomized controlled trials) guidelines. A consort diagram 2010 (flow diagram) of the trial is shown in Figure 1.

Ethics approval and consent of the participants

The study was performed in accordance with the declaration of Helsinki. The trial was conducted as per the international council for harmonisation (ICH) guidelines on good clinical practice (GCP) and meets the requirements of the Indian regulations for carrying out herbal and ayurvedic clinical trials and Ayurveda Siddha Unani-GCP. ICH-GCP issued by U.S. Department of health and human services were followed wherever applicable. The trial was registered with the clinical trials registry (CTRI: CTRI/2018/04/013183) on 11th April 2018 and hosted at ICMR's national institute of medical statistics as per mandate of drugs controller general of India (DCGI, CTRI/2018/04/013183). Trial protocol was approved by Shetty's hospital ethics committee and was conducted at Shetty's hospital in Bangalore, India. Prior to conducting the study, each subject was informed of the study procedures, including potential risks and benefits and prior written consent was obtained from each patient.

Participants

Ambulatory male or female subjects 35-70 years old were screened for the study. Subjects fulfilling the eligibility criteria were recruited for the study.

Eligibility criteria

Eligibility criteria included mild to moderate knee OA clinically detected or diagnosed by X-ray (grade 0, I and II on Kellgren-Lawrence scale; otherwise healthy individuals with no clinically significant or relevant abnormalities except for study related condition(s);primary hypertensive and newly diagnosed type II diabetic patients with first line medication or without medication were included; willingness to refrain from taking ibuprofen , aspirin or other NSAIDS, or any other pain reliever (OTC or prescription) during trial period; female subjects with child-bearing potential only if on birth control; female subjects of non-child bearing potential only if amenorrhoeic for at least 1 year or who had a hysterectomy, bilateral oophorectomy, or tubectomy.

Exclusion criteria

Exclusion criteria included signs or history of dislocations or quadriceps tendons tear; non-degenerative joint disease or other joint diseases; acute or congenital illness; history of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematous, etc, history of knee or hip joint replacement surgery or any hip or back pain that interfered with ambulation; expecting surgery during study duration; history of known allergy to NSAIDs or hypersensitivity, allergy or sensitivity to herbal products; taking acetaminophen/paracetamol, ibuprofen, aspirin or other NSAIDs, or any other pain reliever (OTC or prescription), or any natural health product (excluding vitamins) within 7 days prior to screening; consuming any corticosteroid, indomethacin, glucosamine, or chondroitin within 3 months prior to treatment period; intra-articular treatment or injections with corticosteroid or hyaluronic acid within 6 months of treatment period; evidence or history of clinically significant condition(s) of hematological, renal, pulmonary, gastrointestinal, cardiovascular, hepatic, or neurological diseases,

malignancies or severe thyroid disorders; high alcohol intake (greater than 2 standard drinks per day) or use of recreational drugs such as cocaine, methamphetamine, marijuana, etc.; history of psychiatric disorder that would impair the ability to provide written informed consent; physical disability participation in other trials involving investigational or marketed products within 30 days of screening visit; female subjects who were pregnant, breast feeding, or planning to become pregnant during study period; HIV positive.

Intervention

Karallief easy climb™ (KEC) contains a blend of uniquely standardized proprietary extracts of *Cardiospermum halicacabum, Vitex negundo, Boswellia serrata, Bambusa arundinacea, Citrus sinensis* and *Curcuma longa*. Aerial parts of *Cardiospermum halicacabum* were extracted and standardised for a combination of hydroxy flavone derivatives along with saponins and triterpenoids. Aerial parts of *Vitex negundo* were extracted and standardised for iridoid glycosides along with saponins and flavonoids. Gum resin of *Boswellia serrata* was extracted and standardised for pentacyclic tri-terpenic acids. The siliceous secretion of the shoots of *Bambusa arundinacea* were extracted and standardised for natural silica. Fruit peels of *Citrus sinensis* were extracted and standardised for bioflavonoids. Rhizomes of *Curcuma longa* were extracted and standardised for water soluble saponin glycosides. HEG contains lower amounts of the same herbal ingredients as KEC, with the difference being the addition of glucosamine sulphate, extracted from prawn shells. Both KEC and HEG have a dosage of 500 mg packaged into a gelatine capsule. Daily dosage for both products is 1000 mg. (i.e. 2 capsules per day).

Trial design

Eligible subjects who completed the informed consent were randomized to receive HEG, KEC, or placebo control through a computer-generated randomization code using permuted block design and the block size selected was known only to the statistician until the statistical analysis was completed. Allocation concealment was done by using sequentially numbered opaque sealed envelopes (SNOSE), wherein study subjects, investigators, and sponsor's personnel remained blinded to the medication assignment. 40 subjects were randomly allocated to each group, a total of 120 participants across three groups-group A-HEG, group B-KEC and group C-placebo. Total duration of the study was 120 days with 6 scheduled visits (screening visit, baseline, 30, 60, 90 and 120 days) by the subjects at the clinical centre including screening and randomization day.

Subjects were given their assigned medication at visit 2 (day 1) and asked to take 1 capsule orally, twice daily-after breakfast and after dinner. Subjects were given enough supplements to last until their next visit (visit 3, day 30±3) and asked to record their daily consumption in the diaries provided and on compliance cards. Complete medical history was taken during screening visit. Screening visit and each study visit also included a physical exam, measurement of vital signs, and collection of concomitant medication, concurrent illness, and adverse event information. Blood and urine samples and an X-ray of the knee were collected at the screening visit and final follow-up visit (day 120±3). Each follow up visit (days 30, 60, 90 and 120±3) involved administration of the supplement, assessments of knee osteoarthritis parameters, and collection of safety and tolerability information. At no point in the study, the code was broken, or un-blinded study product was administered to any subject. The investigator was given the right to break the blind in special situations such as: treatment of emergent serious adverse events (SAE) and to protect the safety of the patient.

Compliance and adverse events

At each study visit, extra medication was returned for investigators to confirm that the correct number of supplement capsules had been taken. Subjects requiring additional pain relief were given rescue medication, these subjects were considered treatment failures for the purposes of this study. Laboratory test: complete blood count (CBC), random blood sugar, liver function tests, renal function tests, lipid profile test, serum calcium and phosphorus, c- reactive protein (CRP), RA factor, routine urine analysis were performed at first and last visit. A rapid HIV test and ECG were performed at screening visit. Urine pregnancy testing was performed on females of child-bearing potential at screening visit and visits 3-6. Adverse events were recorded for severity and their relationship to consumption of supplement. All adverse events were followed until they were resolved or stabilized or until they were considered no longer clinically significant by the investigator. In patients who were being actively treated for diabetes or hypertension, drug-drug interactions were considered.

Withdrawal and dropout

Subjects who did not meet inclusion/exclusion criteria were considered screen failures. Participating subjects were allowed to withdraw at any time without the need to justify their decision. Some subjects were unwilling to continue due to relocation and were considered as dropouts. No subjects discontinued or dropped out from study due to non-compliance with medication, protocol violation, worsening of disease or tolerability, SAE or AE.

Primary and secondary outcome measures

The primary endpoint was to compare the improvement in knee OA with HEG or KEC treatment with the placebo as measured by changes in in the 30-second-chair-stand-test (30SCST) scores. The Western Ontario and McMaster universities osteoarthritis index (WOMAC)

was used to assess pain, stiffness, and physical function. Knee flexion test was used for range of movements through goniometry. Anteroposterior (AP) and lateral view X-rays of knee joint was used to confirm diagnosis of OA and measure changes in joint width space from baseline to final visit. Secondary endpoint of the study was to evaluate safety and tolerability of HEG and KEC by measuring vital signs, selected laboratory parameters, and adverse events.

Statistical analysis

Study data collected was assessed using statistical analysis software (SAS) package. All data are expressed as mean ± SEM (standard error of mean) in graphs and mean (standard deviation) in tables. P values were calculated using paired test to compare time points within same group, ANOVA to compare groups at same time point, or ANCOVA using baseline measurement as a covariant when comparing baseline to visit 6 across groups. P<0.05 were considered statistically significant. Missing post-baseline observations were imputed using last observation carried forward approach (LOCF).

All hypothesis was tested at a significant level of 0.05 and 95% confidence interval. Descriptive analysis for baseline summary statistics, including mean, medians and SD for demographic data and proportion of males and females were provided.

RESULTS

Participating subjects and compliance

Of the 130 subjects who participated in the screening visit, 120 subjects qualified for the study based on inclusion/exclusion criteria and signing of the informed consent (Figure 1). These subjects were randomized to one of three groups: group A (HEG), group B (KEC) and group C (placebo).

In total, 16 subjects discontinued the study: 4 from group A, 6 from group B, and 6 from group C (Figure 1). Subjects who completed the study had more than 80% compliance to the supplement dosing schedule. For demographics, see Table 1.

Thirty-second chair stand test

The 30SCST was used as a clinical measure of the subject's strength and endurance. This test consists of the subject standing up and sitting down from a chair as many times as possible in 30 seconds.

At baseline, there was no significant difference in the 30SCST score between groups. Subjects in group A and group B had a significant improvement in their 30SCST when comparing baseline to visit 6, increasing from 11.08±1.48 to 13.08±1.81 (18% increase, p<0.0001) and 11.06±1.18 to 12.86±1.69 (16% increase, p<0.0001) respectively. Placebo group also significantly improved from 11.03±1.55 to 11.88±2.0 (8% increase, p=0.0008). There was a significant difference between baseline and visit 6 across all groups (p=0.0007), with both group A and B significantly increasing over placebo group (p=0.0009 and p=0.0088), but not from each other (p=0.7893) (Figure 2A).

Table 1: Demographic information of subjects meeting the eligibility requirements and who signed the informed consent.

Statistic	Group A HEG	Group B KEC	Group C placebo
Gender	40	40	40
Female			
N (%)	25 (62.50)	23 (57.5)	24 (60.0)
Male			
N (%)	15 (37.5)	17 (42.5)	16 (40.0)
Age at baseline (year)			
Mean ± SD	47.9±8.5	50.7±11.1	47.7±10.1
Median	47	53.5	46.5
Min, Max	35, 68	35, 70	32, 70

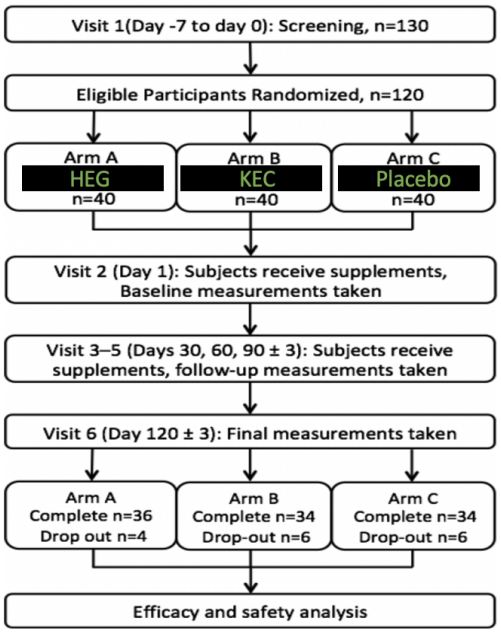

Figure 1: Study design.

A total of 130 subjects were screened for the inclusion and exclusion criteria at the initial visit. Of those screened, 120 subjects were eligible to participate and signed the informed consent. Eligible participants were randomized into one of the three arms of the study, with 40 participants per arm. At the baseline visit (day 1), subjects received the assigned supplement and baseline measurements were taken. Follow up visits occurred every 30 days thereafter, where subjects were allocated supplement and follow-up measurements were taken. The final visit occurred on day 120 and final measurements were taken at this visit. In

total, 104 subjects completed the study and their results were analyzed for efficacy and safety of the assigned supplement.

WOMAC scale assessment of pain, stiffness, and physical function

WOMAC is a self-administered questionnaire consisting of 24 questions that describe subjects' pain, stiffness, and physical functions. It was developed to quantify the symptoms of knee OA. An improvement from baseline would be indicated by a decrease in WOMAC scores.

Pain score (WOMAC A) reduced in all groups: from 5.94±2.59 to 1.58±2.27 (73% reduction, p<0.0001) in group A, from to 5.94±2.22 to 1.74±1.40 (71% reduction, p<0.0001) in group B, and from 4.41±1.88 to 2.24±1.21 (49% reduction, p<0.0001) in placebo group (Figure 2B).

There was a significant difference between all groups from baseline to visit 6 (p=0.0036), with groups A (p=0.0048) and B (p=0.0176) showing a statistically significant difference as compared to placebo.

Stiffness score (WOMAC scale B) was significantly different between groups at the baseline and improved in all groups over time. Group A reduced from 0.50±0.81 to 0.17±0.45 (66%, p=0.0007); group B from 1.03±1.09 to 0.29± 0.68 (71.8%, p<0.0001); and placebo group from 1.09±0.93 to 0.56±0.79 (48.6%, p<0.0001). Though there was reduction in score over time in all groups, the difference was not statistically significant across groups (p=0.0992, Figure 2C). However, there was a decreasing trend observed in ANCOVA p values over time (p=0.8436, p=0.3365, p=0.0992 respectively at visits 4, 5 and 6), suggesting that longer duration may be necessary to observe a statistically significant effect.

Physical function score (WOMAC scale C) was significantly different at baseline, with group B having a higher score compared to groups A or placebo group. Similarly, all groups improved over time: from 13.08±8.41 to 3.53±5.13 in group A (73%, p<0.0001), 15.74±8.78 to 4.85±3.53 in group B (69%, p<0.0001), and 12.21±6.27 to 5.65±2.55 in the placebo group (54%, p<0.0001). There was a significant reduction in score from baseline to visit six across groups (p=0.0122), with group A showing significant difference compared to placebo group (p=0.0109) (Figure 2D).

Knee flexion

The range of knee flexion was measured using goniometry while the subject was lying down. Goniometer was placed on lateral aspect of the leg to be assessed. As the subject flexed their knee, difference between the beginning and end angle measurement was noted. All groups improved significantly over time, increasing their range of flexion. Group A increased from 121.11±7.66° to 128.89±8.38° (6%, p<0.0001), group B increased from 113.68±6.89° to 122.50±6.99° (7.7%, p<0.0001), and placebo group increased from 115.00±6.40° to 119.12±6.91° (3.6%, p<0.0001). Difference in degree of knee flexion from baseline to visit 6 was significantly different across groups (p=0.0001), with both group A (p=0.0005) and group B (p=0.0008) showing statistically significant increased range of movement as compared to placebo control (Figure 2E).

Joint space width in the knee joint

At baseline visit (Day 1, visit 2) and final follow-up visit (day 120±3, visit 6), X- rays of the AP and lateral views of knee were collected to measure minimum joint space width of medial compartment of the tibiofemoral joint. All groups showed improvement in joint space width from baseline to visit 6, with group A improving from 1.58±0.32 mm to 1.95±0.32 mm (23%, p<0.0001), group B from 1.54±0.47 mm to1.92±0.54 mm (25%, p=0.0001) and placebo group from 1.52±0.31 mm to 1.69±0.41 mm (11%, p=0.0013) (Figure 2F). Difference in joint space width from baseline to visit six was significantly different across groups (p=0.0036), with both group A (p=0.0229) and group B (p=0.0339) showing statistically significant increased joint width space compared to placebo control.

Blood tests

At baseline visit (day 1, visit 2) and final follow-up visit (day 120±3, visit 6), approximately 5-8 mL of blood was collected for clinical laboratory evaluation of markers such as serum calcium, alkaline phosphatase (ALP), and C-reactive protein (CRP) associated with OA. Higher serum calcium may reduce the severity of osteoarthritis[15] while CRP and ALP increase with OA progression and the associated inflammation.[16]

There was no statistically significant change in CRP or ALP in groups A and B (Table 2). Serum calcium levels increased in all three arms between baseline readings and visit 6, including a statistically significant increase in group A (4% increase, p=0.0015) and group B (3% increase, p=0.0056), but there was no statistically significant increase in placebo group (p=0.3599, Table 2).

Adverse events and safety

Safety of supplements was measured by recording vital signs, physical examination, clinical laboratory tests, and any adverse events. All parameters were normal and did not significantly change. There were no serious adverse events (SAEs) observed in any subject during this study.

Minor AEs were observed in 19 subjects including gastritis, fever, abdominal bloating, rhinitis, drowsiness, and vomiting. These events were evenly distributed in the three arms-5 in group A, 6 in group B, and 8 in the placebo group. These events were self-limiting and subsided without any intervention. Study physicians prescribed concomitant medication to some subjects for few days. No drug-drug interaction occurred in patients who were being actively treated for diabetes or hypertension.

Table 2: Serum calcium, alkaline phosphatase, and C-reactive protein levels at baseline and at final follow-up visit.

Study arm	Calcium	Alkaline phosphatase	C-reactive protein
Group A			
Baseline	9.41 (±0.51)	78.75 (±13.66)	3.44 (±1.03)
Visit 6	9.82 (±0.50)	80.39 (±12.74)	3.40 (±0.80)
P value	0.0015	0.5808	0.8775
Group B			
Baseline	9.46 (±0.45)	80.68 (±19.29)	3.43 (±0.93)
Visit 6	9.79 (±0.54)	82.15 (±12.88)	3.46 (±0.95)
P value	0.0056	0.6726	0.8761
Placebo			
Baseline	9.50 (±0.56)	78.59 (±10.84)	3.39 (±0.85)
Visit 6	9.62 (±0.51)	74.21 (±11.34)	3.34 (±1.00)
P value	0.3599	0.0459	0.8448

DISCUSSION

This study found that herbal supplements HEG and KEC significantly reduced OA-related knee pain and increased joint mobility when compared to a placebo. Patients in HEG (group A) and KEC (group B) showed significant improvement on 30SCST and WOMAC indices, knee flexion tests, and increase in joint space width compared to the placebo (group C). Also, both supplements were safe and well-tolerated.

The 30SCST was used as a primary end point to measure general joint mobility and stamina. The test measures the number of times that someone can sit and stand in 30-seconds. This test is predictive of falling risk. HEG and KEC were more than twice as effective as the placebo in improving 30SCST scores (Figure 2A), with increases of 18.05%, 16.27%, and 7.71%, respectively. Previous studies have determined that a minimal clinically important difference (MCID) score for the 30SCST is an increase of 2 repetitions, and both proprietary formulas approximately met that criteria, while the placebo did not.[17] According to CDC guidelines, patients in their sixties with 30SCST values less than 13 are at a higher risk of falling.[18] All 3 groups in this study had an average baseline value of around 11. By Day120, both KEC and HEG Groups saw their average 30SCST value rise to 13. In contrast, placebo group was only able to raise the value to 11.8, so patients were still at an elevated risk for falling.

Patients taking HEG and KEC reported significant 73 and 71% reductions in their WOMAC A pain scores, respectively, at day 120, compared to 49% reduction in the placebo group (Figure 2B). At day 30, patients in HEG and KEC groups saw a significant reduction in pain scores, by 23% and 15%, compared to the placebo's value of 2.7%. Clinically, this is significant as patients are more likely to continue taking medication if they experience a tangible reduction in pain sooner.

At baseline, three groups (group A, group B, and group C respectively) had average knee flexion values of 121°, 114°, and 115°. A healthy knee can flex up to 130°, so the difference between a healthy knee and an osteoarthritic knee is about 10-15°.[19] In the knee flexion test, HEG and KEC brought a statistically significant increase of 7.78° and 8.82°, nearly double the 4.12° of the placebos (Figure 2E). A more flexible knee could lead to greater stability and more ease in performing day to day activities.

The two treatment groups also experienced an increase in joint space width. In healthy adults, medial minimum joint space width of tibio-femoral joint is around 4.8-5.7mm.[20] The cartilage helps to keep the bones a normal distance apart. However, in patients with OA, cartilage is damaged and the joint space narrows significantly. Bones may start rubbing against each other, causing pain.

HEG and KEC contributed to a statistically significant increase in joint space width in tibio-femoral joint (23 and 25%) compared to placebo (11%), as seen in X-rays (Figure 2F).

The improvement in knee mobility could be due to supplement's effects in reducing inflammation and initiating tissue repair. The increase in the joint space width seen is an interesting finding. This suggests that, over and beyond pain reduction, some physiological changes could be contributing to the improvement experienced by the patient. The physiological changes could include-repair or regeneration of connective tissue (collagen/cartilage) and/or increase in secretion of lubricating synovial fluid or changes in synovial fluid characteristics.

Such physiology changes could indicate that KEC and HEG may help address the root cause of the Osteoarthritis (joint degeneration) and help in rebuilding the joint. This would be a substantial improvement over commonly used joint supplements today which focus on reducing pain rather than addressing the root cause. Further studies need to be done on KEC and HEG to examine physiological changes (if any).

HEG contains glucosamine sulfate. Glucosamine is thought to reduce cartilage degradation and inflammation in the joint.[22] Many joint supplements contain large amounts of glucosamine, which can cause hyperacidity and ulcers. So, patients may stop taking glucosamine. HEG has lesser glucosamine and KEC has no glucosamine, making gastrointestinal discomfort less likely. In this study, there were some complaints of minor gastritis and abdominal bloating, but none were severe enough to cause patient to stop taking the supplement, and they were also described in patients taking the placebo.

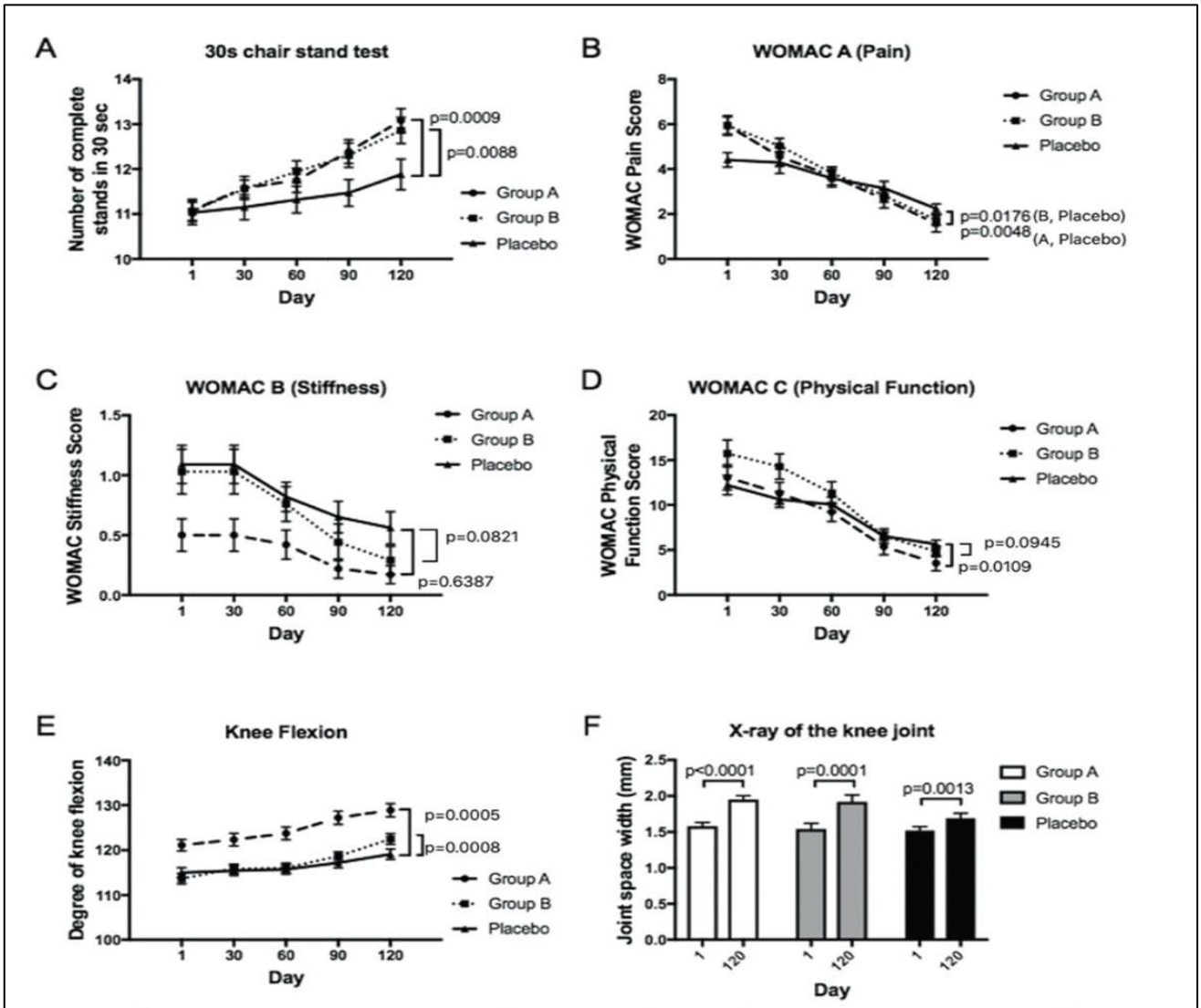

Figure 2: 2A-2F: Comparison of treatment (A&B) with placebo (C) groups. A: 30s chair stand test; B: WOMAC A (pain); C: WOMAC B (Stiffness); D: WOMAC C (Physical function); E: Knee flexion; F: Joint Space. Figures 2A to 2E - Results of the knee osteoarthritis assessments presented as the mean value for each group at each time point ± SEM. P values indicate difference between baseline and visit 6 (day 120) between group A or B and the placebo group after adjusting for the baseline as covariant. Figure (A) Results of the 30-second chair stand test reported as the mean number of completed stands in 30 seconds for each time point. Figures (B-D) Changes in WOMAC score over time for (B) pain, (C) stiffness, and (D) physical function. Figure (E) Changes in the degree of knee flexion measure by goniometry. (F) Changes in joint space width measured by x-ray at visits two and six (days 1 and 120). P values here indicate significant differences between day 1 and day 120 within each group.

Figure 2: Comparison of treatment with placebo groups.

Although we saw improvements in several measurements in placebo group (C), HEG and KEC demonstrated significantly superior results. Importantly, improvements in stiffness and pain relief are frequently observed in placebo groups for osteoarthritis, while measurements of physical function tend not to change with placebo treatment.[4,23] The mechanisms for this placebo effect include expectations by patients of improvement, classic conditioning, contextual healing, response bias, and patient interaction with the practitioner.[4,24] In line with these findings, in this study we found an improvement in pain, stiffness, function and joint space width with placebo treatment, but treatment with HEG and KEC showed significantly greater improvements.

No serious adverse events or changes in vital signs, clinical safety parameters, or physical exams were observed during this trial, but more long-term studies of the efficacy and safety of HEG and KEC are needed to confirm these results. However, potentially substantial risks and side

effects of using OTC or prescription pain medications could be avoided by using natural supplements such as HEG or KEC. Furthermore, these supplements are formulated as easy-to-swallow capsules, compared to often oversized pain medication capsules or tablets that are difficult to swallow. KEC contains entirely vegan products, which makes it accessible to more of the general population.

CONCLUSION

This study demonstrated that natural supplements HEG and KEC improve knee OA symptoms and can be safe and effective treatment option for patients with OA. Since they are natural supplements that can be taken long-term, without side effects associated with other pain medications, they may also be a promising proactive supplement for maintaining joint health in younger populations who have not yet developed OA. More long-term studies are needed to determine preventative capabilities of HEG and KEC, but results of this study support their use in reducing OA pain and improving joint health.

Funding: funding source- Green Chem, Karnataka, India.
Conflict of interest: The authors Rajendran Ramaswamy and Ravikumar Rajendran are affiliated with Green Chem. Krishna Rajendran is affiliated with Karallief Inc. Karallief Inc have applied for trademarks and patents covering HEG and KEC.
Ethical approval: The study was approved by the Institutional Ethics Committee of *Shetty's Hospital, Bangalore, India.*

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Cite this article as: Rajendran K, Vieira KF, Ramaswamy R, Koffie RM, Rajendran R, Berger TR, et al. Assessment of safety and efficacy of Karallief® Easy Climb™, an herbal extract blend for supporting joint health: a double-blind, placebo-controlled, randomized clinical trial. Int J Basic Clin Pharmacol 2021;10:1-9.