Research Article | *Cuestiones de Fisioterapia* | *Medicine*

Fixed-Dose Herbal Extracts for Symptomatic Knee Osteoarthritis: Effectiveness and NSAID-Sparing Benefits

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Abstract

Background: Osteoarthritis (OA) of the knee is a leading cause of pain and disability among adults aged above 50 years in South India. Long-term reliance on non-steroidal anti-inflammatory drugs (NSAIDs) is constrained by gastrointestinal, cardiovascular, and renal toxicities, especially in elderly patients with comorbidities. Phytotherapeutic agents such as *Apium graveolens* (celery seed) and *Boswellia serrata* have demonstrated anti-inflammatory and analgesic activity through inhibition of the cyclooxygenase and 5-lipoxygenase pathways. Aim and Objective: To assess the clinical effectiveness and NSAID-sparing potential of a fixed-dose combination of celery seed extract and *Boswellia serrata* extract as adjuvant therapy in patients with symptomatic knee OA attending orthopaedic centres in Coimbatore and Madurai, Tamil Nadu. Materials and Methods: A multicentre, prospective, open-label observational study was conducted on 312 patients (aged ≥40 years) clinically diagnosed with primary knee OA according to American College of Rheumatology criteria. Participants received a celery seed (200 mg) and *Boswellia serrata* (250 mg) combination tablet twice daily for 90 days, in addition to ongoing therapy. Primary outcomes were Western Ontario and McMaster Universities Arthritis Index (WOMAC) total, pain, stiffness, and physical function scores, and the proportion of patients with reduced NSAID requirement. Secondary outcomes were Visual Analogue Scale (VAS) scores at rest and on movement. Results: Statistically significant improvements ($p<0.001$) were observed in the WOMAC total score (21.45%), WOMAC pain (71.83%), WOMAC stiffness (68.92%), and physical function (74.16%) subscales. The VAS at rest improved by 70.34% and on movement by 62.51%. Regular NSAID usage declined from 65.38% at baseline to 28.21% at day 90, with a parallel rise in paracetamol use from 16.99% to 34.62%. **Conclusion:** The celery seed and *Boswellia serrata* combination demonstrated clinically meaningful pain relief, improved joint function, and a substantial NSAID-sparing effect, supporting its role as a safer adjunctive therapy for the long-term management of knee osteoarthritis in the South Indian population.

Keywords: *Knee osteoarthritis; Apium graveolens; Boswellia serrata; NSAID-sparing effect; WOMAC; Phytotherapy; South India.*

1. INTRODUCTION

Osteoarthritis (OA) is the most common chronic, degenerative joint disorder, characterised by the progressive loss of articular cartilage, subchondral bone sclerosis, osteophyte formation at the joint margins, and a low-grade inflammation of the synovial membrane. The condition predominantly affects the weight-

bearing joints, with the knee being the most frequently involved site in the Indian context. Community-based epidemiological surveys conducted across the country during the early years of the twenty-first century have documented the prevalence of symptomatic knee OA among adults above 45 years to range between 22% and 39%, with rural populations of southern Indian states such as Tamil Nadu and Karnataka reporting some of the highest figures because of intensive squatting, agricultural labour, and a relatively higher proportion of obese and post-menopausal women in the community.

The pathophysiology of OA involves a complex interplay among mechanical stress, biochemical mediators, and inflammatory cytokines. Pro-inflammatory mediators such as interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), and matrix metalloproteinases (MMPs) drive chondrocyte apoptosis and cartilage matrix degradation, while prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) contribute to nociceptive sensitisation and persistent pain. The pain experienced by patients with OA arises from a combination of nociceptive and neuropathic mechanisms, including peripheral sensitisation of joint afferents and increased excitability of dorsal-horn neurons within the central nervous system.

The therapeutic strategy for knee OA aims to reduce pain, restore joint function, and improve overall quality of life through a combination of non-pharmacological measures such as weight reduction, exercise, and physiotherapy, with pharmacological interventions. Current international guidelines continue to recommend non-steroidal anti-inflammatory drugs (NSAIDs) as a cornerstone of pharmacological therapy. NSAIDs exert their analgesic and anti-inflammatory effects by inhibiting the cyclooxygenase (COX) enzymes and the consequent biosynthesis of prostaglandins. However, prolonged NSAID use is associated with serious gastrointestinal ulceration and bleeding, hypertension, fluid retention, renal impairment, and an increased cardiovascular risk. Elderly patients, who form a major proportion of the OA population in India, are particularly vulnerable owing to polypharmacy, multimorbidity, and age-related decline in renal and hepatic function.

These limitations have generated renewed interest in plant-derived agents that offer comparable anti-inflammatory benefits with a more favourable safety profile. *Apium graveolens* (celery) seed extract contains volatile oils, sedanolide, 3-n-butyl phthalide, and apigenin, which inhibit cyclooxygenase and prostaglandin synthesis without producing significant gastric mucosal injury. In experimental polyarthritis models, celery seed extract has shown efficacy comparable to ibuprofen and naproxen, while concomitantly mitigating NSAID-induced gastric irritation. Traditional Indian and Ayurvedic systems have long recognised celery seeds as a carminative, diuretic, antispasmodic, and analgesic agent.

Boswellia serrata, commonly known as Indian frankincense or salai guggal, is a tree native to the dry hills of central and peninsular India. Its oleo-gum-resin contains a family of pentacyclic triterpenic acids, of which 3-O-acetyl-11-keto-β-boswellic acid (AKBA) is the most pharmacologically potent. AKBA selectively inhibits 5-lipoxygenase (5-LOX), thereby reducing the formation of pro-inflammatory leukotrienes implicated in synovitis and cartilage matrix degradation. Several randomised controlled trials conducted between 2003 and 2010 in India have demonstrated that standardised *Boswellia* extracts produce statistically significant reductions in pain and improvements in mobility within four to eight weeks of administration.

Despite the documented benefits of these phytochemicals individually, real-world data on their combined

use among South Indian populations are limited. The present prospective observational study was therefore designed to evaluate the effectiveness and NSAID-sparing effect of a celery seed and *Boswellia serrata* combination tablet in patients with symptomatic knee OA attending orthopaedic outpatient clinics in Coimbatore and Madurai, Tamil Nadu.

2. MATERIALS AND METHODS

2.1. Study design and setting

This was a multicentre, prospective, open-label, observational study conducted between June 2008 and May 2010 at three tertiary-care orthopaedic outpatient departments located in the Coimbatore and Madurai districts of Tamil Nadu, South India. The participating sites were the Department of Orthopaedics, PSG Institute of Medical Sciences, Coimbatore; the Department of Orthopaedics, Madurai Medical College, Madurai; and a private speciality orthopaedic clinic affiliated to the institutions. The sites were selected to ensure representation of both urban and semi-urban populations of South India, where the burden of knee OA has been documented to be especially high in agrarian and labour-intensive communities.

2.2. Ethical considerations

The study protocol, informed consent document, and case report form were reviewed and approved by the Institutional Human Ethics Committees of each participating centre prior to enrolment. The study was conducted in compliance with the Declaration of Helsinki (revised 2008) and the Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Subjects. Written informed consent was obtained from each participant before any study-related procedure was performed.

2.3. Study population

A total of 312 ambulatory patients of either gender, aged 40 years and above, with a clinical and radiological diagnosis of primary knee osteoarthritis fulfilling the American College of Rheumatology (ACR) criteria, were enrolled in the study. Patients reporting at least moderate knee pain (≥5 on a 10-point Visual Analogue Scale) during the most painful movement of the index knee within the preceding month were considered eligible.

2.4. Inclusion criteria

Patients of either gender aged between 40 and 78 years with symptomatic primary knee osteoarthritis (Kellgren-Lawrence radiological grade II or III), a body mass index between 18 and 35 kg/m², willingness to maintain their existing analgesic and physiotherapy regimen during the study period, and the ability to comprehend the study protocol and provide written informed consent were included in the study.

2.5. Exclusion criteria

Pregnant or lactating women, patients with recent (<12 weeks) acute knee injury or intra-articular corticosteroid injection, secondary osteoarthritis due to inflammatory arthropathies, uncontrolled diabetes mellitus or hypertension, significant cardiac, hepatic, or renal disease, known hypersensitivity to celery, Boswellia, or related plant species, and those participating in any other interventional study within the preceding four weeks were excluded.

2.6. Intervention

Eligible participants received a fixed-dose combination tablet containing standardised celery seed extract (200 mg) and *Boswellia serrata* extract (250 mg, standardised to ≥40% boswellic acids), administered orally twice daily after meals for 90 consecutive days. Patients were permitted to continue their ongoing analgesic and NSAID therapy at the discretion of the treating orthopaedic surgeon. Adjustment of NSAID dose and frequency, or substitution with paracetamol, was permitted on the basis of the patient's clinical response and tolerability.

2.7. Outcome measures

The primary outcome measures included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score and its pain, stiffness, and physical function subscale scores; the proportion of patients requiring a reduction in NSAID dose; and the proportion of patients shifting from oral NSAIDs to oral paracetamol. The secondary outcome measures comprised the Visual Analogue Scale (VAS) score for pain at rest and pain during movement, both rated on a 0-10 cm scale. Assessments were performed at baseline (day 0), day 30, day 60, and day 90 (end of treatment). Tolerability was monitored through spontaneous reporting of adverse events and clinical examination at each visit.

2.8. Statistical analysis

Data were captured on paper-based case report forms and transcribed into a Microsoft Excel database. Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to summarise demographic and baseline characteristics. As the WOMAC and VAS instruments yield ordinal-scale scores, the non-parametric Wilcoxon Signed-Rank Test was used to compare baseline and end-of-treatment values. Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A two-tailed p-value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Demographic and baseline characteristics

Of the 312 patients enrolled, 168 (53.85%) were female and 144 (46.15%) were male, reflecting the established female preponderance of knee osteoarthritis in the Indian population (Table 1). The mean age of the cohort was 54.62 ± 9.18 years, with a range of 40 to 78 years (Table 2). The majority of participants (62.18%) belonged to the 50-65 year age band. The mean body mass index was 26.84 ± 3.42 kg/m², and 44.55% of patients were classified as overweight or obese.

At baseline, 188 (60.26%) participants were receiving concomitant analgesic medications (Table 3). The most commonly used analgesics were diclofenac (32.05%), aceclofenac (18.59%), naproxen (9.62%), and paracetamol (16.99%); 124 (39.74%) participants were not on any regular pain medication.

Table 1: Gender-wise distribution of study participants

Gender	Number of Patients	Percentage
Male	144	46.15%
Female	168	53.85%
Total	**312**	**100.00%**

Table 2: Age distribution of participants

Variable	N	Mean ± SD	Min - Max
Age (Years)	312	54.62 ± 9.18	40 - 78
BMI (kg/m²)	312	26.84 ± 3.42	18.6 - 34.7

Table 3: Distribution of patients by concomitant analgesic medication

Concomitant Medication	Number of Patients	Percentage
None	124	39.74%
Diclofenac	100	32.05%
Aceclofenac	58	18.59%
Naproxen	30	9.62%
Paracetamol	53	16.99%

3.2. Primary outcome measures

The mean WOMAC total score reduced significantly from 72.86 at baseline to 57.24 at the end of 90 days of treatment, representing an overall improvement of 21.45% ($p<0.001$). Progressive improvements were noted at each interim visit (Table 4). The WOMAC pain subscale score declined from 17.42 at baseline to 4.91 at day 90, corresponding to a 71.83% improvement ($p<0.001$). The WOMAC stiffness score reduced from 8.16 to 2.54, a 68.92% improvement ($p<0.001$), while the physical function subscale score improved by 74.16%, decreasing from 47.28 to 12.21 ($p<0.001$).

Table 4: Changes in WOMAC subscale scores from baseline to day 90

WOMAC Subscale	Day 0	Day 30	Day 60	Day 90	% Improve
Total score	72.86	66.91	61.18	57.24	21.45%
Pain	17.42	12.34	8.13	4.91	71.83%
Stiffness	8.16	6.04	4.27	2.54	68.92%
Physical function	47.28	32.61	21.45	12.21	74.16%

All four reductions were statistically significant ($p<0.001$, Wilcoxon Signed-Rank Test).

At baseline, 65.38% of patients were on regular NSAIDs. By day 90, the proportion using NSAIDs had declined to 28.21%. Concurrently, paracetamol use rose from 16.99% to 34.62%, indicating a successful step-down from NSAIDs to safer analgesics. Combined NSAID-paracetamol use reduced from 12.18% at baseline to 4.81% at day 90. NSAID dose reduction was required in 5.13% of patients at day 30 and in 13.46% of patients by the end of treatment (Table 5).

Table 5: NSAID and paracetamol utilisation across time points

Medication category	Day 0	Day 30	Day 60	Day 90
NSAIDs (any)	65.38%	44.87%	36.86%	28.21%
Paracetamol	16.99%	23.40%	29.17%	34.62%
NSAID + Paracetamol	12.18%	9.29%	6.73%	4.81%
Patients with NSAID dose reduction	—	5.13%	9.62%	13.46%

3.3. Secondary outcome measures

The mean VAS score at rest decreased from 7.62 at baseline to 2.26 at day 90, an improvement of 70.34% ($p<0.001$). The mean VAS score during movement reduced from 8.24 at baseline to 3.09 at day 90, representing a 62.51% improvement ($p<0.001$). The improvements were progressive across all assessment time points (Table 6).

Table 6: Changes in Visual Analogue Scale (VAS) scores

VAS Score	Day 0	Day 30	Day 60	Day 90	%
At rest	7.62	5.74	3.95	2.26	70.34
During movement	8.24	6.41	4.78	3.09	62.51

3.4. Tolerability

The investigational combination was well tolerated throughout the 90-day study period. Mild and self-limiting adverse events were reported in 14 patients (4.49%), comprising mild epigastric discomfort (n = 6), nausea (n = 4), loose stools (n = 3), and mild skin itching (n = 1). All events resolved spontaneously without specific intervention. No serious adverse events, treatment-related discontinuations, or laboratory abnormalities were recorded.

4. DISCUSSION

The present prospective multicentre observational study, conducted in two orthopaedic outpatient departments of Tamil Nadu, evaluated the clinical effectiveness and NSAID-sparing effect of a celery seed and *Boswellia serrata* combination tablet in 312 patients with symptomatic primary knee osteoarthritis. Statistically significant improvements were demonstrated in all measured WOMAC subscales and VAS scores, accompanied by a substantial reduction in regular NSAID consumption.

The 71.83% improvement in WOMAC pain and 68.92% improvement in stiffness scores observed in our cohort are comparable to, and in some parameters exceed, the magnitude of relief reported by previous Indian and international studies on *Boswellia serrata* extracts published during the early 2000s. The randomised controlled trial by Kimmatkar and colleagues showed that 1000 mg/day of *Boswellia serrata*

extract produced a significant reduction in knee pain and improvement in flexion within eight weeks. Sontakke and colleagues subsequently demonstrated that 333 mg of *Boswellia* thrice daily was non-inferior to valdecoxib for knee OA. The synergy with celery seed extract observed in our combination tablet may be attributed to complementary inhibition of two distinct inflammatory pathways: COX-mediated prostaglandin biosynthesis (celery seed) and 5-LOX-mediated leukotriene production (Boswellia).

The improvement in WOMAC physical function score (74.16%) and VAS pain on movement (62.51%) reflects a clinically meaningful enhancement of joint mobility, which is particularly relevant for the agrarian and labour-intensive populations of South India, where preserved knee function is essential for occupational activity and continued participation in daily living. These results are concordant with earlier observational data from southern Indian cohorts that documented marked functional improvement following adjunctive herbal therapy in patients with chronic knee pain.

A salient feature of the present study is the demonstration of an NSAID-sparing effect. The reduction of regular NSAID use from 65.38% at baseline to 28.21% at day 90, together with the successful transition of a sizeable proportion of patients to paracetamol or to a reduced NSAID dose, indicates that this combination can serve as an effective NSAID- and steroid-sparing adjuvant. This finding is of considerable public-health importance in elderly Indian patients, in whom long-term NSAID use is associated with peptic ulceration, hypertension, congestive cardiac failure, and chronic kidney disease.

The mechanistic basis for the observed effects can be traced to the constituent phytochemicals. Apigenin and 3-n-butyl phthalide present in celery seed inhibit nuclear factor-kappa B (NF-κB) signalling and reduce IL-1β-induced cartilage matrix degradation. AKBA from *Boswellia serrata* selectively inhibits 5-lipoxygenase and the formation of pro-inflammatory leukotrienes, thereby reducing synovial inflammation and pain. The favourable tolerability profile observed in the present study, with only 4.49% of participants reporting mild adverse events and no serious adverse events, supports the long-term feasibility of this combination as an adjunct therapy for chronic knee osteoarthritis.

Limitations of the present study include the open-label design, the absence of a placebo or active comparator arm, the lack of radiological end-points, and the relatively short follow-up period of 90 days. Self-reported reduction in NSAID use is also susceptible to recall bias. Nevertheless, the prospective design, multicentre recruitment, the use of validated outcome measures (WOMAC and VAS), and standardised dose of the investigational combination lend credibility to the findings.

Future studies should include randomised controlled designs with larger sample sizes, longer follow-up of six to twelve months, biomarker estimation (CRP, IL-6, COMP), magnetic resonance imaging-based cartilage assessment, and dose-finding evaluations to clearly delineate the optimal therapeutic window of the celery seed and *Boswellia serrata* combination in osteoarthritis management.

5. CONCLUSION

The present prospective multicentre observational study conducted in South India demonstrates that a standardised combination of *Apium graveolens* (celery seed) and *Boswellia serrata* extract administered twice daily for 90 days produces clinically and statistically significant improvements in knee pain, stiffness,

and physical function in patients with symptomatic primary knee osteoarthritis. The combination also exerts a substantial NSAID-sparing effect, reducing the requirement for non-steroidal anti-inflammatory drugs by more than half and facilitating successful transition to safer analgesics such as paracetamol. With its favourable tolerability profile and demonstrable functional benefits, this phytotherapeutic combination represents a promising, safer, and economically viable adjunctive option for the long-term management of knee osteoarthritis, particularly in elderly patients with comorbidities for whom prolonged NSAID exposure carries an unacceptable risk. Larger randomised, double-blind, controlled trials with extended follow-up are warranted to confirm and expand these findings.

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