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## Clinical effectiveness and tolerability of Celery seed and Boswellia serrata extract in osteoarthritis

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### Abstract

**Background:** Osteoarthritis (OA) is a common chronic articular degenerative disease marked by articular cartilage degradation, synovial inflammation/immunity, and subchondral bone lesion, among other symptoms. The disease affects 2–6% of the global population, and its prevalence increases with age, reaching 40% in people over the age of 70. Recently, there has been a surge of interest in using nutraceuticals to treat or prevent OA. Celery seed extract & Shallaki extracts (*Boswellia serrata*) effectively prevent cardiovascular disease, urinary tract infection, gout, and improve blood pressure. Experimental results indicate that both these extracts have anti-inflammatory properties.

**Aim:** The current real-world evidence study was conducted to investigate the effectiveness of Celeract Advance Tablet in OA patients.

**Methods:** A total of 1236 patients were enrolled in the study. All patients received Celeract Advance Tablet for 90 days. Clinical assessment of symptoms included palpation tiredness, mobility limitation, joint crepitus, swelling and redness. Osteoarthritis symptoms were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Total European Quality of Life–5 Dimensions and visual analogue scale (VAS).

**Results:** After 90 days treatment with Celeract Advance Tablet, WOMAC score reduced significantly from 62.64 + 20.47 to 17.22 + 17.59 ( $p < 0.05$ ). For Total European Quality of Life–5 Dimensions (EQ-5D) score significantly improved from 38.76 + 8.10 to 69.13 + 8.60 ( $p < 0.05$ ). From the baseline, 78.35% improvement in EQ-5D was observed in patients treated for three months. After 90 days, VAS score for pain significantly reduced from 8.07 + 5.38 to 1.78 + 4.46 ( $P < 0.05$ ) after 90 days in OA patients. No major adverse reactions were reported.

**Conclusion:** The current study revealed that the Celeract Advance tablet effectively improves joint pain, stiffness, physical function and quality of life in OA patients.

**Keywords:** Osteoarthritis, Celery seed extract, Shallaki extracts, anti-inflammatory, NSAIDs, Apiaceae

### Introduction

Osteoarthritis (OA) is a chronic pain condition affecting an individual's quality of life. OA is the most frequent cause of musculoskeletal pain [1]. In geriatric patients above 60 years of age, the prevalence of OA is more in men (10%) than women (13%). About 10-15% of geriatric patients show signs and symptoms of OA, with a higher prevalence in women compared to men. In India, the prevalence of OA is higher in the rural population (56.6%) than urban (32.6%). Due to lifestyle changes, the Asian population is highly exposed to the risk of knee osteoarthritis compared to Europeans and Americans [2, 3, 4]. The pain in osteoarthritis is caused by multiple factors driven by nociceptive and neuropathic mechanisms, along with abnormal pain pathways of the peripheral and central nervous system (CNS). Inflammation in the joint initiates a cascade of events which leads to increased sensitivity of nociceptive primary afferent neurons, peripheral sensitization, and hyper-excitability of the nociceptive neurons in the CNS [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the management of arthritic stiffness and other rheumatic diseases [6]. Although NSAIDs are recommended by clinical guidelines for managing pain and inflammation in OA (first-line treatment), NSAIDs show various adverse effects, including cardiovascular, renal, hepatic and gastrointestinal [1, 6].

A celery seed extract has anti-inflammatory, analgesic, and gastro-protective properties.

Celery preparations have been used extensively since ancient times as natural therapies for the management of acute and chronic painful or inflammatory conditions [7]. The celery plant (*Apium graveolens*) is an indigenous plant from the family Apiaceae. The plant has a broad spectrum of use as an aphrodisiac, anthelmintic, carminative, diuretic, emmenagogue, laxative, antispasmodic sedative, stimulant, and toxin [8].

*Boswellia serrata*, also known as Shallaki, is a tropical plant in the Burseraceae family. They are flowering plants of medium size, both trees and shrubs. The fragrant resin produced by the plant is used to make frankincense. *Boswellia* is widely used in traditional medicine and is an essential component of ayurvedic medicine. Different studies showed that *Boswellia* extract and its components possess pharmacological properties such as antioxidant, anti-inflammatory and anti-tumor action. It also exerted a positive effect on aging, diabetes, cardiovascular and neurodegenerative disease [9].

The current study was conducted to evaluate the efficacy of Celeract Advance Tablet in OA patients.

## Methods

### Study Design

A multicenter, Prospective, real-world evidence study of Tablet Celeract Advance™ (manufactured by Wallace Pharmaceuticals Pvt. Ltd.) was conducted to evaluate the effectiveness and tolerability in osteoarthritis patients.

### Settings and participants

Patients aged between 19 to 75 years with the clinical diagnosis of osteoarthritis of the knee based on the American College of Rheumatology (ACR) criteria and at least moderate pain in the knee (rated at 5 or greater by the subject on a visual analog scale) during the most painful knee movement during the last month and inadequately controlled with NSAIDs were recruited for the study.

Patients who had uncontrolled diabetes, hypertension, hepatic disorder, pregnant & lactating women, and acute joint trauma of the knee were excluded from the study.

### Study intervention

During the study, the enrolled subjects were treated with Celeract Advance Tablet [Celery Seeds (Ajamoda Extract) 250 mg and Shallaki Extract (*Boswellia serrata*) 300 mg] twice daily for three months. Patients were advised not to consume other ayurvedic, herbal, and homeopathic treatments during the study period. The record of concomitant medication was maintained during the study.

## Outcome and follow up

The primary objective was to evaluate the OA symptoms, WOMAC score, and pain during the study. Pain on palpation, limited mobility, joint crepitus, edema, and redness were all graded on a 4-point scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe). The Western Ontario and McMaster Universities (WOMAC) osteoarthritis index was used to quantify the severity of osteoarthritis symptoms, with a higher WOMAC score indicating more severe symptoms. The subjects rated their discomfort on a 10-mm visual analog scale (VAS). On days 0, 30, 60, and 90, the WOMAC, pain, and OA symptoms were evaluated. On day 90, the patient's global assessment and the physician's global assessment were evaluated.

## Statistical Analysis

Demographic data were analyzed using descriptive statistics. The Difference in clinical response before and after the treatment was assessed for normal distribution using the Kolmogorov Smirnov test. The paired Student's t-test was also used. For distribution-free data, the Mann Whitney U test was used. All tests were carried out at 5% significance.

## Results

During the study, a total of 1236 patients were enrolled based on inclusion and exclusion criteria, comprising 504 (41%) males and 732 (59%) females. The mean age of the subject was 54.22 years, and 37.73% of patients belong to the age group above 50 years. All the subjects selected during the study subjects received Celeract Advance Tablet twice daily for three months.

## Primary Outcome Measures

### WOMAC score

At the baseline, the mean WOMAC combined score was  $62.64 \pm 20.47$  ( $p < 0.05$ ), which was reduced significantly to  $17.22 \pm 17.59$  ( $p < 0.05$ ) at the end of the study. From the baseline, 72.50% improvement in WOMAC score was observed in the patients after treatment with Celeract Advance Tablet (Figure 1).

Further sub-group analysis shows 34.90% of patients had excellent improvement, 25.83% and 20.81% of patients had marked and moderate improvement respectively in WOMAC score after 90 days of treatment with Celeract Advance Tablet (Table 1). The improvement in WOMAC score of OA patients was observed within a month after treatment with Celeract Advance Tablet™

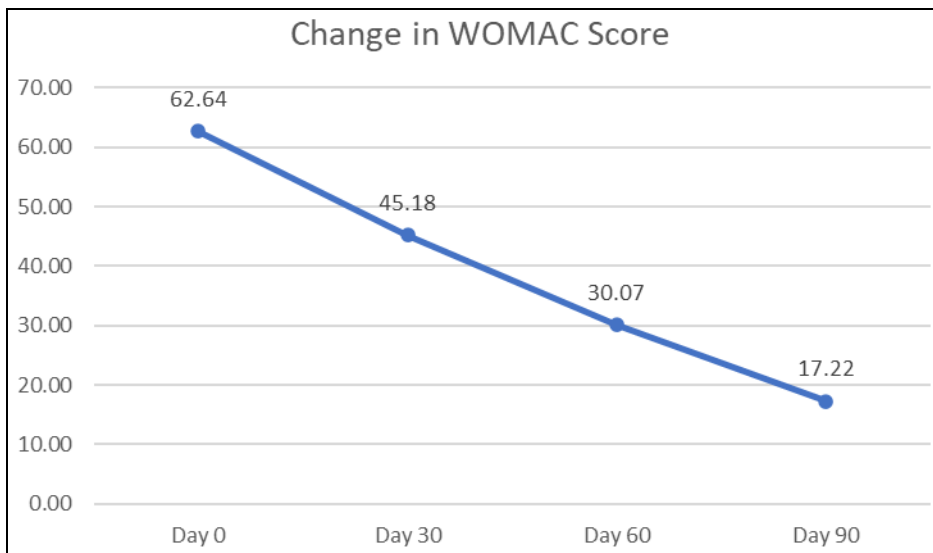


Fig 1: Change in WOMAC score during the treatment

Table 1: Overall effect on WOMAC score

Overall Effect WOMAC	No of Patients	Percentage
Excellent improvement (>90%)	431	34.90%
Marked improvement (75-89%)	319	25.83%
Moderate improvement (51-74%)	257	20.81%

**Total European Quality of Life–5 Dimensions (EQ-5D)**

**Score:** After 90 days of treatment with Celeract Advance Tablet total ED-5D score significantly improved from 38.76 + 8.10 to 69.13 + 8.60 ( $p < 0.05$ ). From the baseline, 78.35% improvement was observed in patients treated for three months (Figure 2).

Excellent improvement was observed in 37.09% of patients, 27.45%, and 21.30% of patients had marked and moderate improvement in total EQ-5D score (Table 2).

The total EQ-5D score increased significantly after three months of treatment [38.76 + 69.13 to 69.13 + 8.60 ( $p < 0.05$ )].

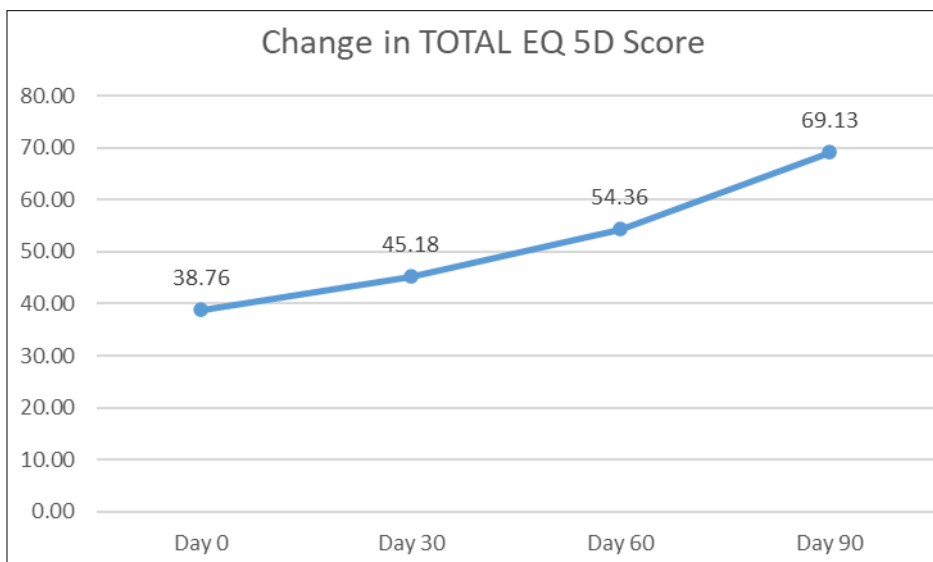


Fig 2: Change in Total EQ 5D score during the treatment

Table 2: Overall effect on Total EQ 5D score

Overall Effect TOTAL EQ 5D	No of Patients	Percentage
Excellent Improvement (>90%)	458	37.09%
Marked Improvement (75-89%)	339	27.45%
Moderate Improvement (51-74%)	263	21.30%

**Secondary Outcome measures**

**VAS score**

VAS score is generally used to determine the intensity of pain in patients. Celeract Advance Tablet treatment reduced VAS score from 8.07 + 5.38 to 1.78 + 4.46 ( $P < 0.05$ ) after 90 days

in OA patients (figure 3).

Furthermore, the sub-analysis evaluation revealed excellent improvement of VAS score in 37.41% of patients, while 27.94% and 21.78% of the patients showed marked and moderate improvement, respectively (Table 3).

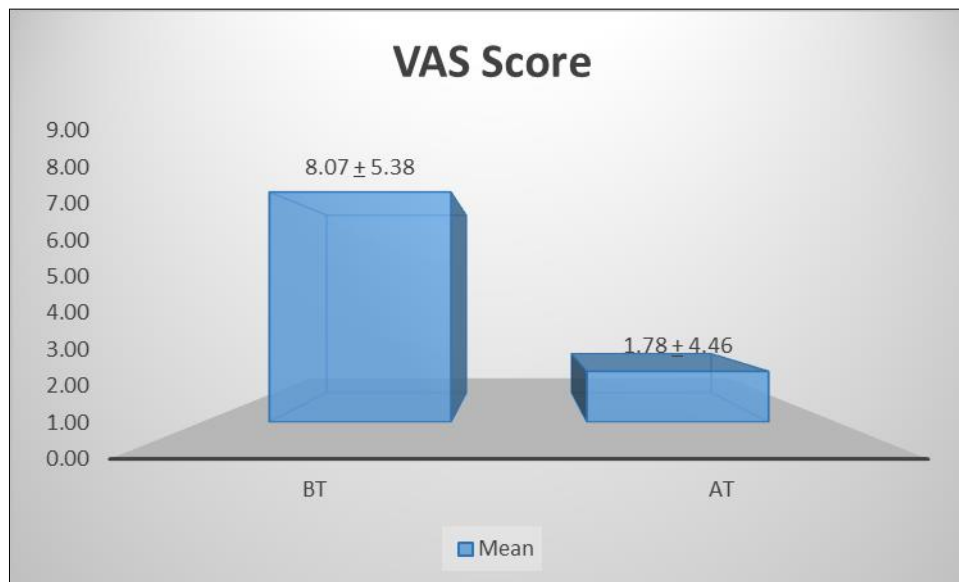


Fig 3: Change in VAS score during the treatment

Table 3: Overall effect on VAS score for pain

Overall Effect VAS	No of Patients	Percentage
Excellent improvement (>90%)	462	37.41%
Marked improvement (75-89%)	345	27.94%
Moderate Improvement (51-74%)	269	21.78%

### Discussion

This Multicenter, Prospective study investigated the effectiveness of Celeract Advance Tablet in patients with osteoarthritis. The administration of Celeract Advance Tablet for three months lead to the improvement in WOMAC score, total EQ-5D score, and VAS score in OA patients. The improvement in OA was observed a month after initiation of treatment with Celeract Advance Tablet. The results obtained in the current study are in line with a similar published open-label study involving adult patients with chronic inflammatory conditions such as osteoarthritis and rheumatoid arthritis. In the study, patients received 250 mg tablets containing standardized celery seed extract twice daily for 8 weeks. Excellent improvement in the reduction of joint swelling was seen in 45% of the patients; 46% of the patients showed good improvement in reducing grinding/cracking knees on movement; 42% showed excellent efficacy in reducing the restriction of movements; 49% showed good improvement in reduction of morning stiffness and pain during movements and 57% showed good improvement in reducing the difficulty in doing daily chores. The administration of celery seed extract tablets twice daily for 8 weeks was effective and well-tolerated in OA patients [10].

Celery preparations have been used majorly for the management of acute and chronic inflammatory conditions. Celery Seed Extract (CSE) has similar efficacy as aspirin, ibuprofen, and naproxen in suppressing arthritis in a model of polyarthritis and has also been proven as an analgesic in two experimental models. CSE also protect against and/or reduce gastric irritation caused by NSAIDs, and act synergistically with them in reducing inflammation [7].

Celery seed inhibits COX 1 and 2 and prostaglandin synthesis. Pre-clinical studies have shown similar efficacy of celery seed extract and ibuprofen in reducing inflammation. A 12-week study was conducted in OA patients. The patients received a celery extract tablet twice daily. The study showed that after 3 weeks of the treatment, there was a 68% reduction in pain scores, with 100% pain relief in some patients. Those

who continued treatment for 6 weeks showed maximum benefits. Another study was conducted with patients receiving the higher dose of the extract (75 mg). The study reported statistically significant reductions in pain scores, mobility, and quality of life. Another clinical study in patients with OA found 75% relief in pain in patients receiving the celery seed extract as compared to placebo [7, 8, 10].

3-O-Acetyl-11-keto-beta-boswellic acid (AKBA) in *Boswellia serrata* extract contributes to its anti-inflammatory action by inhibiting 5-lipoxygenase. A meta-analysis of 28 studies found that *Boswellia serrata* extract is both safe and effective in patients with OA [11].

### Conclusion

This is the first clinical evidence generation study that supports the potential use of Celeract Advance, a novel combination of Celery seed (*Ajmoda*) extract and Sallaki (*Boswellia serrata*) extract as an adjuvant in the management of knee OA. Celeract Advance helps in the improvement of joint pain, stiffness and function, thus leading to a better quality of life in patients with OA.

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