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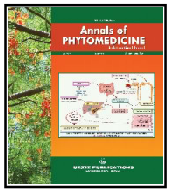

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# Effectiveness of *Boswellia serrata* Roxb. extract on osteoarthritis treatment: A systematic review of randomized controlled trials

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**Abstract**

Osteoarthritis (OA) is a prevalent condition affecting knee joints, given that traditional treatments such as NSAIDs pose risks. *Boswellia* extract emerges as a promising alternative due to its anti-inflammatory properties, yet its efficacy remains understudied in knee osteoarthritis. The aim of this systematic review is to assess the effectiveness of *Boswellia* compared to placebo and NSAIDs for knee OA management. A systematic search was conducted for non-pharmacological treatments for knee OA. The focus was on *Boswellia* extract, and the search included randomized controlled trials (RCTs) and English articles published between January 10, 2003 and March 4, 2023. Thirty-nine studies were selected, screened, and systematically analysed to assess the efficacy of *Boswellia* extract. The results of the studies suggested that *Boswellia* extract combinations could be a valuable addition to drug treatment regimens for knee OA. They indicate reductions in pain, improvements in function, and decreased risk of adverse events. Future research should evaluate the efficacy and safety of *Boswellia* extract over longer periods in knee OA patients.

## 1. Introduction

Osteoarthritis (OA) stands as one of the most common degenerative articular disorders, significantly impacting patients' quality of life (Kan *et al.,* 2019; Umar *et al.,* 2014). Approximately 40% of individuals aged 70 years or older are affected by knee OA, with women being more predisposed than men (Primorac *et al.,* 2020). Age plays a pivotal role in OA incidence, alongside factors such as obesity, genetics, and a history of knee trauma (Liu *et al.,* 2018). Knee OA prevails in about 85% of cases (Michael *et al.,* 2010), with patients commonly experiencing joint pain and instability, morning stiffness, crepitus, and reduced daily physical activity (Dantas *et al.,* 2021). Exercise, weight loss, and patient education constitute the cornerstone of OA treatment (Cao *et al.,* 2020).

In line with guidelines, pharmacotherapy for OA includes acetaminophen, NSAIDs (non-steroidal anti-inflammatory drugs), opioids, and intra-articular injections of glucocorticoids and hyaluronic acid. Despite the temporary improvement in pain and physical function these drugs offer, knee pain and joint stiffness persist in some patients. Moreover, long-term NSAIDs use is associated with an elevated risk of renal insufficiency, gastrointestinal bleeding, hypertension, and congestive heart failure (Dantas *et al.,* 2021). Given the high incidence of adverse events linked to NSAIDs therapy, there is a pressing need for effective and safer alternative treatments for managing OA pain (Bamne *et al.*, 2023).

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The gum resin extracted from the ancient herb *Boswellia* has garnered considerable attention recently as a potent anti-inflammatory, antiarthritic, and analgesic agent. *Boswellia* extract's anti-inflammatory activity is attributed to boswellic acids, particularly 3-O-acetyl-11-keto-beta-boswellic acid (AKBA), which serves as a potent inhibitor of 5-lipoxygenase (5-LOX), a key enzyme in the biosynthesis of leukotrienes from arachidonic acid in the cellular inflammatory cascade (Houssen *et al.,* 2010). Several independent clinical studies support *Boswellia* extract's anti-inflammatory and antiarthritic properties (Joos *et al.,* 2006; Mehta *et al.,* 2016). *In vitro* studies have demonstrated *Boswellia* extract's marked inhibitory effect on both the classical and alternative pathways of the complement system (Knaus and Wagner, 1996; Tiwari *et al.,* 2023; Barman *et al*. 2021).

Clinical studies have shown that *Boswellia serrata* Roxb. (*B. serrata*) extract possesses anti-inflammatory and antiarthritis properties and improves pain and physical function (Gupta *et al.,* 2011). Boswellic acid, a pentacyclic triterpenoid, and its acetylated derivatives affect both the production of antibodies and cell-mediated immunity (Safayhi *et al.,* 1992). Collectively, these studies suggest that *B. serrata* may offer therapeutic effects that help alleviate symptoms, potentially surpassing conventional NSAIDs therapy, particularly considering evidence suggesting that some NSAIDs may adversely affect cartilage metabolism over time, in addition to the known toxicity associated with conventional NSAIDs (Attri *et al.*, 2023; Sharma and Roy, 2022).

The historical use of *B. serrata* for pain relief, coupled with recent findings indicating that these phytochemicals may act directly on several inflammatory processes, provides compelling evidence that these products can alleviate pain and may slow cartilage deterioration in patients with knee osteoarthritis. However, very few randomized controlled trials (RCTs) have examined the efficacy of *B. serrata*

formulations in humans with knee osteoarthritis. Therefore, the aim of this systematic review is to evaluate the effectiveness of *B. serrata* extract on its own and compare it to placebo and NSAIDs for the knee joint.

## 2. Materials and Methods

### 2.1 Search strategy

We searched for studies on non-pharmacological treatments for OA. We examined randomized controlled trials (RCTs) and articles published in English between January 10, 2003 and March 4, 2023. Thirty-nine studies were selected from PubMed, Wiley online library, and other databases including PubMed, Scopus, Web of science, and Cochrane. The search was conducted using the keywords "*Boswellia*" or "*Boswellia* extract" and "knee osteoarthritis" or "knee OA." All identified papers underwent screening first by title and then by abstract, followed by full-text screening. Inclusion criteria were articles written in English and based on human trials investigating the treatment of knee osteoarthritis with *Boswellia* extract. Patients included in the trials were suffering from knee osteoarthritis for at least three months and were treated with *Boswellia* extract. A systematic approach was employed to evaluate the evidence regarding the use of *Boswellia* extract in treating knee OA.

### 2.2 Study selection

Randomized controlled trials comparing combinations of *Boswellia* extracts given alone against placebo or NSAIDs were included. Exclusion criteria comprised non-randomized study designs, treatment protocols allowing concomitant medications like NSAIDs or other analgesics (unless used as rescue drugs), and interventions involving additional nutrients or herbal supplements. Participants were diagnosed with knee osteoarthritis based on specific criteria. Intervention methods involved *B. serrata* extract, with comparison methods including other treatments for knee osteoarthritis, such as placebo or conventional medicine. The selection process is described in Figure 1.

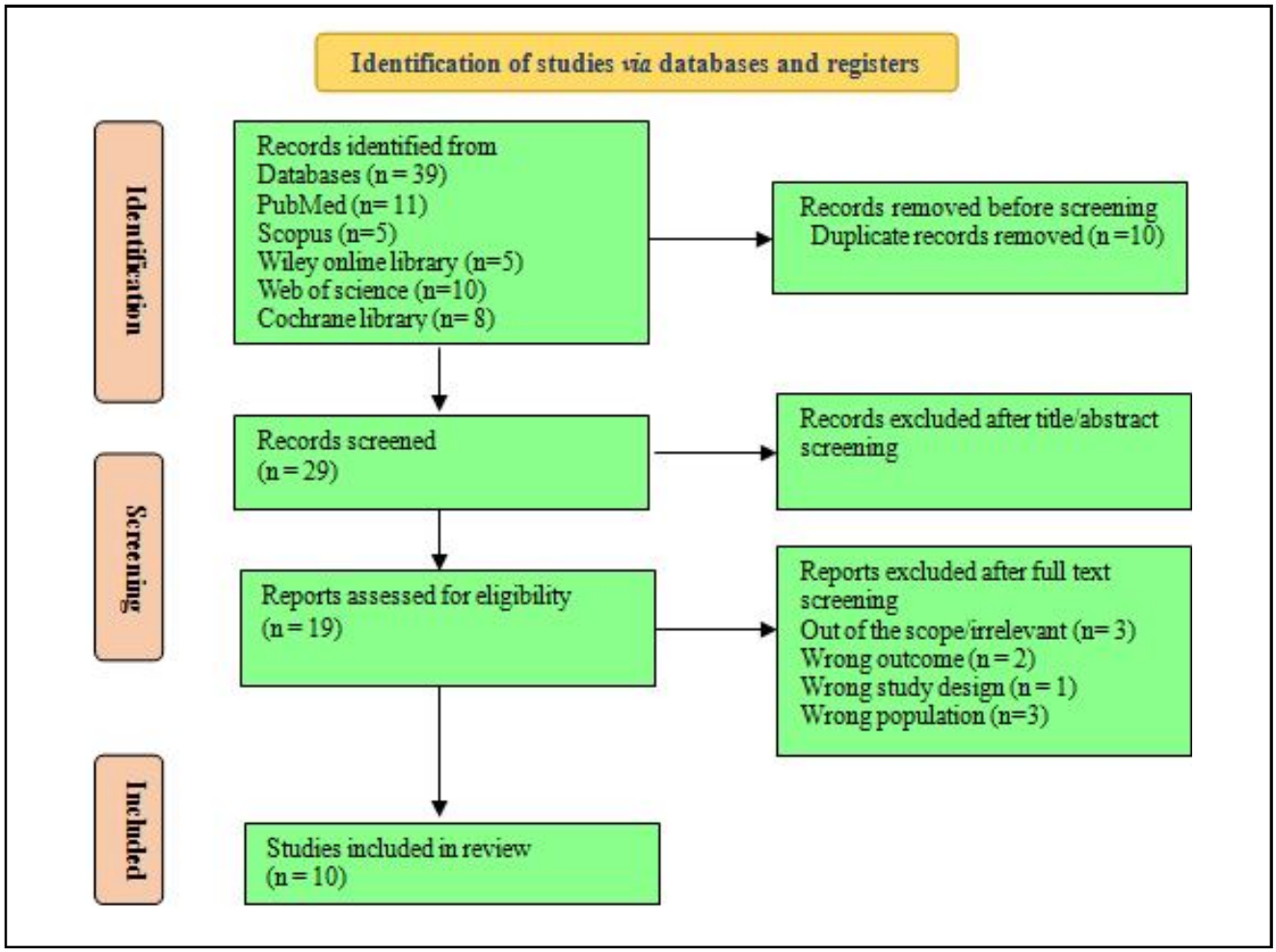


**Figure 1: Flow diagram showing the screening process and the search results.**

## 3. Results

The systematic search identified a total of 39 relevant publications through database searching. Among these, 10 publications met the inclusion criteria. Seven randomized clinical trials compared *Boswellia* extract against a placebo (Tables 1, 2, 3) while one trial compared *B. serrata* extract against Valdecoxib, a non-steroidal anti-inflammatory drug (Table 2). Additionally, one trial compared solid lipid *B. serrata* particles against standardized *B. serrata* gum extract (Table 3). The final study was an observational trial that tested *Boswellia* derivatives in combination with physical exercise (Table 2).

**Table 1: The characteristics of the included studies M-Male; F-Female; OA-Osteoarthritis; WOMAC-Western Ontario and McMaster Universities; LFI- Lequesne's Functional Index; VAS- Visual analog scale; BSE-*Boswellia* serrata extract; MMP-3 -matrix metalloproteinase-3; TNFα-Tumor necrosis factor.**

| Subject characteristic | Study design and duration | Dose | Measurement | Aim | Outcome | References |
|---|---|---|---|---|---|---|
| **N=30**<br>(12 M/18 F)<br>**Age 45-72**<br>Non-hypersensitivity to NSAIDs<br>Symptoms of osteoarthritis of the knee | **Crossover study**<br>Intervention for 8 weeks with a washout period of 21 days was given at the end of the first intervention.<br>Use a WOMAC questionnaire. | **Group 1**:<br>333 mg of BSE, one capsule three times a day.<br>**Group 2:**<br>Placebo containing starch powder. | 1.Questionnaire (WOMAC).<br>2-Pre and post-intervention radiographs. | To assess the efficacy, safety, and tolerability of BSE in OA knee. | 1-The decrease in severity of pain and swelling and improvement in the loss of function were clinically and statistically significant ($p$ <0.001) in the group receiving the active drug as compared to the group receiving the placebo.<br>2-Radiologically there was no change. | **Kimmatkar *et al.*, 2003**<br>India |
| **N =70**<br>(20 M/50 F)<br>**Age 40-80**<br>Symptoms of moderate to mild OA | **Parallel study**<br>Intervention for 12 weeks was assessed at baseline and on each follow-up visit (days 7, 30, 60 and 90.<br>Use a (WOMAC) questionnaire. | **Group 1**:<br>*B. serrata* extract 5-Loxin (100 mg/day) capsules<br>**Group 2:** 5-Loxin )250 mg/day( capsules<br>**Group 3:**<br>Placebo group two capsules of rice bran. | 1-Knee joint synovial fluid for evaluation of MMP-3 concentration.<br>2-a (WOMAC) questionnaire-based assessment of pain, stiffness, and physical function | To evaluate the efficacy and safety of 5-Loxin® in the treatment of osteoarthritis (OA) of the knee. | 1- 5-Loxin exhibited highly significant reductions in MMP-3 in synovial fluid.<br>2-The two doses of 5-Loxin gave clinically and statistically significant improvements in pain scores and physical ability scores in OA patients, but the high-dose group (250 mg 5-Loxin) showed improvements higher than the 5-Loxin group (100 mg/day) with statistical significance in all the teachers. | **Sengupta *et al.*, 2008**<br>India |
| **N =57**<br>(19 M/38F)<br>**Age 40-80**<br>Subjects suffering for more than 3 months with medial tibiofemoral OA. | **Parallel study**<br>Intervention for 12 weeks<br>assessed at baseline and on each follow-up visit (days 7, 30, 60 and 90.<br>using LFI Index, WOMAC Index. | **Group 1**: (100 mg) of 5-Loxin capsules.<br>**Group 2:** (100 mg) of Aflapin capsules.<br>**Group 3:**<br>Placebo group two capsules of suitable excipient. | 1-Using LFI Index, WOMAC Index Questionnaire<br>2-Evaluate whether 5-Loxin and Aflapin can modulate MMP-3 secretion in TNFα. | To evaluate the comparative efficacy and tolerability of 5-Loxin® and Aflapin® in the treatment of OA of the knee. | 1- Both the treatments with 5-Loxin® and Aflapin® conferred clinically and statistically significant improvements in pain scores and physical ability scores in OA subjects but Aflapin® treatment groups exhibited improvement in pain scores and physical ability scores as early as 7 days after the start of treatment.<br>2-Aflapin provided better efficacy than 5-Loxin in inhibiting MMP-3 secretion from TNFα-induced human chondrocytes. | **Sengupta *et al.*, 2010**<br>India |
| **N =59**<br>(22 M/37 F)<br>**Age 40-80**<br>Suffering from unilateral or bilateral OA of the knee. | **Parallel study**<br>Intervention for 4 weeks<br>the baseline evaluation and during each follow-up evaluation on days 5, 15 and 30.<br>using LFI Index, WOMAC Index, VAS Index. | **Group 1:**<br>Capsule (100 mg) of Aflapin.<br>**Group 2:**<br>Placebo group two capsules having similar organoleptic. | 1-Using LFI Index, WOMAC Index, VAS Index to assess pain, stiffness, and physical function. | 1-To evaluate, the anti-OA efficacy of Aflapin<br>2-To assess whether Aflapin supplementation can provide fast relief from clinical symptoms of OA. | 1-Significant reduction in all the pain scores was observed in the Aflapin group by day 30, when compared to the placebo group.<br>1- Significant reductions in VAS and LFI scores were also observed in Aflapin group over placebo by day 5. | **Vishal *et al.*, 2011**<br>India |

**Table 2: The characteristics of the included studies M-Male; F-Female'; OA-Osteoarthritis; WOMAC-Western Ontario and McMaster Universities; LFI-Lequesne's Functional Index; VAS-visual analog scale; BSE-*Boswellia serrata* extract; MMP-3-matrix metalloproteinase-3; TNFα-Tumor necrosis factor; hs-CRP - high-sensitivity C-reactive protein**

| Subject characteristic | Study design and duration | Dose | Measurement | Aim | Outcome | References |
|---|---|---|---|---|---|---|
| **N =66**<br>**Age 40-70**<br>Symptoms of primary OA of knee | **Parallel study**<br>Intervention for 24 weeks assessed by WOMAC scale at monthly intervals and at the end of study. | **Group 1:** *Boswellia serrata* extract (BSE) 333 mg of BSE thrice daily.<br>**Group 2:** Once daily valdecoxib 10 mg. | 1-Index (WOMAC) scale<br>2-Radiographs | To compare the efficacy, safety, and tolerability of *Boswellia serrata* extract (BSE) in osteoarthritis (OA) knee with valdecoxib, a selective COX-2 inhibitor. | 1-In BSE group, the difference in WOMAC scores was not statistically significant at the end of first month of intervention when compared to baseline ($p$>0.05). But from second month onwards the decrease was highly significant ($p$<0.001) as compared to the baseline and remained so throughout the intervention and even one month after the stoppage of the treatment.<br>1-In valdecoxib group, the decrease in WOMAC scores was statistically significant at the end of one month of treatment as compared to baseline ($p$<0.001) and persisted as long as the treatment was continued.<br>2- There was no difference in the pre- and post-drug radiographs of the affected knee joint. | **Sontakke *et al.*, 2006**<br>India |
| **N =48**<br>(17 M/31 F)<br>**Age 35-75**<br>Newly diagnosed or untreated patients with OA of the knee, with mild to moderate in severity and who were not on any other treatment in the past 3 months. | **Parallel study**<br>Intervention for 16 weeks evaluate the efficacy of at Days 0, 30, 60, 90, and 120. The WOMAC questionnaire | **Group 1:** Two tablets of 169.33 mg of BSE each day.<br>**Group 2:** Placebo group. | 1-A (WOMAC) Questionnaire<br>2-radiography<br>3-the 6-min walk test was to evaluate the effect of BSE on the ability of the patients to walk as far as possible for 6 min.<br>4-Elevated levels of hs-CRP | To evaluate the safety and efficacy of a standardized oral supplementation of Boswellin | 1-BSE treatment group showed a statistically significant decrease in WOMAC score indicating improvements in physical function by reducing pain and stiffness.<br>2-Examination of radiological X-ray images change in the OA condition could be seen where the gap between the knee joints increased.<br>3-the trend in walking had improved significantly ($p$ < 0.01) in patients of the BSE treatment group.<br>4-significant decrease in the activity of hs-CRP in the BSE-treated group was observed in contrast to that from the placebo receiving group. | **Muhammed Majeed *et al.*, 2018**<br>India |
| **N = 70**<br>(13 M/57 F)<br>**Age 40-90**<br>Painful knee for a period of 48 h after physical activity; absence of knee injuries at least 6 months before; compliance with physical exercise during the healthcare program. | **Observational study**<br>Intervention for 12 weeks the study involved numerical comparisons between 3 sets of data from the same patients, recorded during 3 different visits. | *Boswellia* derivates 2 tablets per day were given for 3 months' period. | 1-Assessment (VASA, the WOMAC scale, LFI) | To assess the role of *Boswellia* derivates tablets in the rehabilitation of the clinical and functional status of patients with knee OA. | 1- Comparing the values recorded for the flexion angle among the three visits the observed a steady increase in the values, the overall differences being highly significant. | **Rodica Traistaru *et al.*, 2018**<br>Romania |

**Table 3:** The characteristics of the included studies M- Male; F- Female; OA- Osteoarthritis; WOMAC- Western Ontario and McMaster Universities; LFI- Lequesne's Functional Index; VAS- visual analog scale; BSE- *Boswellia serrata* extract; MMP-3 - matrix metalloproteinase-3 ; TNFα- Tumor necrosis factor ; hs-CRP - high-sensitivity C-reactive protein ; IFN-α- Interferon gamma ; IL-2 - Interleukin 2, IL-4 - Interleukin 4 - IL-6 , Interleukin 6 ; BS Boswellin Super ; JKOM , Japanese Knee Osteoarthritis Measure ; SLBSP Solid lipid *Boswellia serrata* particles ; CTX-II, C-terminal telopeptide

| Subject characteristic | Study design and duration | Dose | Measurement | Aim | Outcome | References |
|---|---|---|---|---|---|---|
| **N= 40**<br>(10 M/30 F)<br>**Age 40-60**<br>Symptomatic unilateral or bilateral osteoarthritis of the knee | **Parallel study**<br>Intervention for 8 weeks parameters were recorded at baseline (before the start of treatment) and at 1 month and 2 months after initiating treatment with SLBSP. | **Group 1**: Capsule 333 mg of standardized BSE.<br>**Group 2**: Capsule 333 mg of the SLBSP. | 1-WOMAC, VAS.<br>2-Level of CTX-II in urine<br>3-serum levels of inflammatory cytokines including IL-2, IL-4, IL-6, TNF-α, and IFN-γ were measured initially. | To investigate the efficacy of SLBSP vs. standardized BSE for symptomatic knee osteoarthritis (OA) treatment. | 1- Both treatments resulted in marked improvement in pain and function scores compared to baseline<br>1-in the VAS score from baseline to second month was 40% in SLBSP arm and 34% in the BSE arm.<br>2-No significant difference was observed in urine CTX-II levels be- tween the two arms at the end of treatment.<br>3-SLBSP caused marked lowering of IL-2 and IL-4 levels as compared to baseline. | **Preeti D. Kulkarni *et al.*, 2020**<br>India |
| **N =70**<br>(8 M/62 F)<br>**Age 41-77**<br>Pain score>4 based on Visual Analogue Scale (VAS) | **Parallel study**<br>Intervention for 8 weeks Patients were asked to apply the solution on the involved knee, three times daily for 4 weeks. | **Group 1:** Oily solution 100 ml of Boswellia solution, 1 g of dried extract of frankincense was added to 20 ml of black seed oil on the involved knee three times daily for four weeks.<br>**Group 2:** The placebo solution with 20 ml of black seed oil and 80 ml of olive oil. | 1-Pain severity based on VAS, the scores of WOMAC. | Topical solution of Frankincense extract could decrease pain severity and stiffness of knee. | 1- The end-of-intervention values for all parameters and scores were significantly lower in drug group than placebo group ($p$<0.001 for all), showing more effectiveness of drug compared to placebo. | **Afsaneh Mohsenzadeh *et al.*, 2023**<br>Iran |
| **N =48**<br>(8 M/62 F)<br>**Age 40-60**<br>Trial recruited Japanese adults with knee pain. | **Parallel study**<br>Intervention for 8 weeks visited Medical Clinic three times (week 0, week 4, and week 8). | **Group 1:** Boswellin Super (BS) one capsule daily (300.00 mg).<br>**Group 2:** Placebo group Starch syrup of reduced malt sugar and another ingredient. | 1-Scale (VAS), (JKOM), (WOMAC)<br>2- high sensitivity C-reactive protein were measured as secondary outcome measures. | The trial investigated the use of Boswellin Super (BS) to relieve knee pain. | 1-In the BS group, there were significant differences compared with week 0 and week 8 in the VAS score, JKOM total score, and WOMAC total score<br>2- Between-group comparison showed a lower hs-CRP levels at week 8 in the BS group than that in the placebo group. | **Muhammed Majeed *et al.*, 2016**<br>India |

### 3.1 *Boswellia* extract vs placebo

#### 3.1.1 Treatment of osteoarthritis of knee

Seven randomized clinical trials compared *Boswellia* extract against placebo in the treatment of osteoarthritis of the knee. A randomized, double-blind, placebo-controlled trial conducted in India showed that Thirty patients consumed (333 mg) of *Boswellia* extract for eight weeks compared to the placebo in patients with osteoarthritis of the knee, used WOMAC (Western Ontario and McMaster Universities is a scale of symptoms and physical disability) to assess pain, stiffness, and physical function; the result was decreased knee pain, increased knee flexion, increased walking distance as well as reduced swelling in the knee joint, and improved loss of function (Kimmatkaret *et al.,* 2003).

Seventy patients participated in a randomized, double-blind study (Sengupta *et al.,* 2008) that used two different doses of 5-Loxin (a novel *B. serrata* extract enriched with 30% 3-O-acetyl-11-keto-beta-boswellic acid) (AKBA): 100 mg/day and 250 mg/day, compared to the placebo for the treatment of knee osteoarthritis. Both doses showed clinical and statistical improvements in pain scores and physical ability in patients with knee osteoarthritis. However, the dose of 250 mg provided faster pain relief than the 100 mg dose. Additionally, the effectiveness of 5-Loxin in reducing the synovial fluid of the knee joint was tested to evaluate the concentration of MMP-3 (known as matrix metalloproteinase-3, actively involved in joint destruction in arthritis patients) as a possible cause of the inflammatory process in the joints. The result showed a significant decrease in MMP-3 in the synovial fluid and pain relief.

In a randomized, double-blind, placebo-controlled clinical trial involving seventy patients (Afsaneh *et al.,* 2023), *B. serrata* extract was used, and 20 ml of black seed oil was added as an external cream to the affected knee for 4 weeks, compared to the placebo. Pain intensity scores were assessed based on VAS (visual analog scale, a measure for acute and chronic pain), WOMAC, and PGA (global physician assessment used to determine a single estimate of the patient's overall severity of disease at a given point in time). For all evaluated scales, the end-of-intervention values were significantly lower in the drug group than the placebo group ($p$<0.001 for all), showing the greater effectiveness of *B. serrata* extract compared to the placebo (Sengupta *et al.,* 2010).

A randomized, double-blind, placebo-controlled study involving fifty-seven patients used two strains of *B. serrata* extract and tested their efficacy in treating and relieving knee pain in patients with osteoarthritis. The first type, 100 mg of 5-Loxin, and the second type, 100 mg of Aflapin (a novel synergistic composition derived from *B. serrata* gum resin containing at least 20% AKBA non-volatile oil), were used against a placebo for 12 weeks. The study utilized the LFI (Lequesne's Functional Index of severity for osteoarthritis) and the WOMAC Index Survey to assess the effectiveness of the treatment. Both 5-Loxin and Aflapin provided clinically and statistically significant improvements in pain scores and physical ability scores (WOMAC, LFI index). Interestingly, significant improvements in pain score and functional ability were recorded as early as 7 days in the treatment group with 100 mg of Aflapin. When tested to evaluate whether 5-Loxin and Aflapin can modulate the secretion of MMP-3 in TNFα (a powerful pro-inflammatory agent that regulates many facets of macrophage function), Aflapin showed 41.36% better efficacy than 5-Loxin in inhibiting MMP-3 secretion from TNFα-induced human chondrocytes.

Furthermore, Vishal *et al.* (2011) used Aflapin (100 mg) against a placebo in a 4-week double-blind, randomized, placebo-controlled clinical study involving fifty-nine patients. The study utilized the LFI Index, WOMAC Index, and VAS Index to assess pain, stiffness, and physical function. The results showed a significant reduction in all pain scores in the Aflapin group by day 30 compared to the placebo group. Interestingly, significant reductions in VAS and LFI scores were also observed in the Aflapin group over the placebo by day 5. The evaluation was conducted during each follow-up on days 5, 15, and 30.

Muhammed Majeed *et al.* (2016) used boswellin super (BS) (a standardized extract from the gum resin of *B. serrata* containing boswellic acids) at a dose of 300 mg for 8 weeks in a randomized, double-blind, placebo-controlled trial involving forty-eight patients. The primary outcome measures, visual analog scale (VAS), the Japanese knee osteoarthritis measure (JKOM) (a tool for evaluating functional status in patients with knee osteoarthritis), and Index (WOMAC), were used to evaluate knee pain. The results showed that the BSE group patients exhibited significant improvements in the VAS, JKOM, and WOMAC scores after 8 weeks of intervention. High-sensitivity C-reactive protein (associated with local inflammatory findings in patients with osteoarthritis) was used as secondary outcome measures; high-sensitivity C-reactive protein levels were lower in the BS group than those in the placebo group after 8 weeks of intervention. This may play a vital role in alleviating pain in the knee joint.

Moreover, Muhammad Majeed *et al.* (2018) conducted a pilot trial with forty-eight patients using an extract named boswellin (a novel extract of *B. serrata*, BSE, containing boswellic acids) in a randomized, double-blind, placebo-controlled trial. The dose administered was 300 mg for 16 weeks compared to the placebo. The WOMAC questionnaire was used to test physical function, pain, and stiffness. The results showed that the BSE treatment group exhibited a statistically significant decrease in the WOMAC score, indicating improvements in physical function by reducing pain and stiffness. Additionally, the 6-minute walk test was utilized to assess the effect of BSE on patients' ability to walk as far as possible for 6 minutes, with a significant improvement observed in walking distance ($p$< 0.01) in the BSE treatment group patients. In the final evaluation by Muhammad Majeed *et al*. (2018), radiography was used, and changes in the X-ray images showed an increased gap between the knee joints, indicating relief from pain.

An observational study conducted in Romania by Rodica Traistaru *et al.* (2018) hypothesized that combining *Boswellia* tablets and rehabilitation methods (ultrasound, physical exercise) could lead to optimal healthcare for knee osteoarthritis patients. The research involved seventy patients, all diagnosed with knee osteoarthritis, who met inclusion criteria such as being diagnosed with primary osteoarthritis, experiencing knee pain within 48 hours after physical activity, and having no knee injuries for at least 6 months. Compliance with physical exercise during the healthcare program was also considered. The VAS Scale and the WOMAC scale were used to assess the impact of the disease on performing daily activities, while the lequesne functional index assessed the therapy's effectiveness. Evaluations were conducted at three phases: initial (T1), after 3 months (T2), and after 6 months (T3). The study aimed to achieve various therapeutic goals with Boswellia, including controlling the painful condition, inflammation, restoring knee stability and mobility,

maintaining knee function, correcting abnormal gait, restoring normal gait, and improving motor control and quality of life. The study confirmed the anti-inflammatory activity of *Boswellia* derivatives in reducing inflammation and pain and observed a steady increase in flexion angle values between the three visits, with overall differences being significant (Friedmann $p<0.001$). Thus, *Boswellia* derivatives, combined with exercise, may contribute to relieving pain in people with knee osteoarthritis.

Preeti de Kulkarni *et al.* (2020) conducted a randomized, double-blind, placebo-controlled study involving forty patients for 8 weeks to investigate the efficacy of solid lipid *B. serrata* particles (SLBSP) (stearic acid added to *B. serrata* extract) versus standard *B. serrata* extract (BSE) for treating symptomatic knee osteoarthritis (OA). Solid lipid *B. serrata* particles were developed to enhance bioavailability for better pain relief results. WOMAC and VAS indices were used, and the level of CTX-II (used to determine cartilage turnover status) in urine and serum levels of inflammatory cytokines, including IL-2, IL-4, IL-6, TNF-α, and IFN-γ, were assessed. Both treatments resulted in marked improvements in pain and function scores compared to baseline at one month and two months, respectively. However, no significant difference in WOMAC scores was observed between the two groups. For the VAS index, both treatments caused significant improvements in the VAS score compared to the baseline. The overall decrease in the VAS score from baseline to the second month was 40% in SLBSP and 34% in the BSE group. While no significant difference was observed in urine CTX-II levels between the treatments, SLBSP caused a marked lowering of IL-2 and IL-4 levels compared to baseline, whereas IL-2 and IL-4 levels increased significantly in the BSE group. IFN-γ levels increased in both groups, but the increase was higher in the BSE group, with a statistically significant difference between the two groups. IL-6 levels increased, and TNF-α levels decreased in both groups compared to baseline, with no significant difference between the two groups. Improvement in symptom scores corresponded to a decrease in the use of rescue analgesics for breakthrough arthritic pain, with SLBSP showing superiority in reducing the need for rescue medications compared to BSE.

### 3.2 *Boswellia* extract vs NSAIDs

Prolonged use of NSAIDs for people with knee osteoarthritis is required for sustained pain relief, but they are associated with adverse drug effects. Therefore, long-term use of NSAIDs has harmful side effects on patients' health. In a study conducted in India by Sontakke *et al.* (2006), a randomized, prospective, open-label, comparative study compared the efficacy, safety, and tolerability of BSE (333 mg) with valdecoxib (10 mg) in 66 patients with OA of the knee over six months. The WOMAC scale assessed the patients at baseline and then at monthly intervals until one month after drug discontinuation. Antero-posterior radiographs of the affected knee joint were taken at baseline and after 6 months.

In the BSE group, the difference in WOMAC scores was not statistically significant at the end of the first month of intervention compared to baseline ($p>0.05$). However, from the second month onwards, the decrease was highly significant ($p<0.001$) compared to baseline and remained so throughout the intervention and even one month after the stoppage of treatment. In the valdecoxib group, the decrease in WOMAC scores was statistically significant at the end of one month of treatment compared to baseline ($p<0.001$) and persisted as long as the treatment was continued. However, for the radiographs, there was no difference in the radiographs before and after treatment of the affected knee joint.

From the results of this study, which is the only one to compare *B. serrata* extract with the analgesic drug valdecoxib, it can be concluded that BES has a slower onset and takes more than a month to appear. At the same time, its analgesic and pain-reducing effect persisted even one month after treatment discontinuation. This is a valuable result because most of the drugs currently used for osteoarthritis patients from modern medicine provide short-term relief of symptoms, as seen in the valdecoxib group, where the onset of effect was rapid but rapidly diminished when treatment was discontinued.

## 4. Discussion

This systematic review includes 10 randomized controlled trials, which compared the efficacy of *B. serrata* extract in knee osteoarthritis both on its own and in comparison, to placebo and NSAIDs for the knee joint. *B. serrata* extract has the potential to relieve pain (VAS and WOMAC), stiffness (WOMAC stiffness), and improve joint function (WOMAC function and Lequesne index) specifically. The amount of *B. serrata* extract in randomized controlled trials ranged from 100-300 mg. Based on the trials used in this systematic review, pain, stiffness, and joint function improved after 4 weeks of continuous *B. serrata* extract intake. Although, this result appears promising, it must be interpreted carefully and cautiously in terms of *B. serrata* safety, attrition bias (incomplete outcome data), and the possibility of a small number of participants.

In terms of efficacy, formulations of *B. serrata* given as treatment are significantly more effective than placebo in relieving symptoms of Osteoarthritis of the knee and do not pose significant safety risks based on accompanying analyses in the studies used. Our results also indicate that formulations of *B. serrata* have similar efficacy profiles to NSAIDs treatments, with significantly fewer adverse events.

An 8-week study in India reported a crossover of participants being given 333 mg of BSE versus a placebo. Before starting and at the end of the first and second interventions, the patients were asked to grade the pain intensity, loss of function, and swelling. Radiographs were also taken at these points. A washout period of 21 days was given at the end of the first intervention to ensure that the residual effect of the first intervention did not linger and affect the second one. After the interventions in the group receiving the active drug, all patients reported a decrease in knee pain, increased knee flexion, increased walking distance, improvement in the capacity of climbing stairs, better ability in kneeling, crossed-legged sitting, and squatting. The knee range of movement was improved, and the frequency of swelling in the knee joint decreased. Radiologically, there was no change. This study was the only one to focus on the washout period to ensure that any further effects on the drug's efficacy were eliminated. It helped to note *Boswellia's* effectiveness in relieving all parameters of patients' pain and stiffness more accurately (Kimmatkar *et al.,* 2003).

Speaking of *Boswellia* extracts, three randomized controlled trials reported testing the efficacy of 5-Loxin® and Aflapin®, a new synergistic formulation derived from *B. serrata* gum resin. Each extract was separately tested against a placebo, compared against each other, and against placebo to test its efficacy in relieving pain in

patients with Osteoarthritis of the knee. Sengupta et al. (2008) reported the use of 5-Loxin in two different doses versus a placebo trial in the treatment of Osteoarthritis. Both doses of 5-Loxin conferred clinically and statistically significant improvements in pain scores and physical ability scores, but the improvement was noticeable in joint function and showed better therapeutic efficacy at 250 mg/day than at 100 mg/day. Pain relief was quick, as early as a week after treatment. It is possible to conclude that the use of the extract in doses higher than 100 mg/day contributes to faster relief of symptoms, but these doses must be tested further to ensure their safety.

In the efficacy test of Aflapin at a dose of 100 mg for 30 days versus placebo, a significant reduction in all pain scores was observed in the Aflapin group by day 30, compared to the placebo group. Subjects in the Aflapin group reported no significant adverse effects. However, the safety and efficacy of Aflapin cannot be fully confirmed due to the short duration of the study. However, the effectiveness of pain relief has been proven in this short period, which is considered one of the impressive results. Nevertheless, more tests are needed to ensure its effectiveness (Vishal *et al.,* 2011).

In comparing the effectiveness of 5-Loxin and Aflapin versus placebo, both treatments with 5-Loxin® and Aflapin® conferred clinically and statistically significant improvements in pain scores and physical ability scores. However, Aflapin exhibited better therapeutic efficacy over 5-Loxin® at 100 mg/day; it reduces pain rapidly, as early as after 1 week of treatment. Thus, we conclude the rapid effectiveness of Aflapin as an agent in relieving symptoms of knee osteoarthritis compared to 5-Loxin (Sengupta *et al.,* 2010).

Elevated levels of hs-CRP are found to be associated with local inflammation in patients with OA. Several studies have shown that hs-CRP is elevated in the plasma of patients with OA compared with age-matched controls (Pearle *et al.,* 2007). In a discussion of the effect of the levels of hs-CRP, two randomized controlled trials reported on Boswellin® (BS), which is a standardized extract of B. serrata gum containing boswellic acids. The results of these two studies showed the efficacy of Boswellin as a potent inhibitor of hs-CRP induced local inflammation in patients with knee OA, in addition to contributing to the reduction of all levels of pain among the participants (Muhammed Majeed *et al.,* 2018; Muhammed Majeed *et al.,* 2016).

When comparing the use of *B. serrata* extract versus the analgesic drug valdecoxib, which is a selective inhibitor of COX-2, the results of a 7-month study testing the extract against the analgesic drug showed clear results on the effectiveness of the extract against the analgesic drug. The extract was superior to valdecoxib, except for a slower onset compared to valdecoxib. While BSE showed a slower onset of effect, the effect persisted even after stopping treatment, whereas the effect of valdecoxib became apparent faster but diminished rapidly after stopping treatment (Sontakke *et al.,* 2006). However, several studies should be conducted comparing the efficacy and safety of *Boswellia* extract and *Boswellia* versus analgesic medications for patients with knee osteoarthritis.

A study conducted by Rodica Traistaru *et al.* (2018) hypothesized that the use of *Boswellia* derivative tablets in addition to rehabilitation methods (ultrasound and physical exercises) would provide optimal healthcare for knee OA patients. The results of the study showed positive results in relieving pain resulting from osteoarthritis of the knee, enhancing the natural strength and flexibility of the muscles, and improving the movement of the knee. As the treatment of exercises in addition to *Boswellia* improved the effectiveness of *Boswellia* for elderly patients with osteoarthritis of the knee. However, this study is considered weak due to the lack of a placebo-controlled group. Therefore, studies testing the enhancing efficacy of using Boswellia as a treatment for knee osteoarthritis should be conducted in combination with a physical exercise program.

Previous studies showed that *Boswellia* compounds KBA and AKBA have low bioavailability and reported lower plasma concentrations in human volunteers, while another study showed that no AKBA was detected in plasma (Sharma *et al.,* 2004; Sterk *et al.,* 2004). To circumvent this, a solid lipid from *B. serrata* was developed to improve bioavailability. Where Preeti D. Kulkarni *et al.* (2020) tested the efficacy of *B. serrata* magnetic lipid particles (SLBSP) versus *B. serrata* Standard (BSE) extracts. Results of both products containing *B. serrata* extract significantly improved symptoms of osteoarthritis in the knee during the 2-month study period, with no significant difference between groups. However, SLBSP demonstrated superior efficacy by significantly reducing the need for rescue analgesics during treatment with SLBSP compared to BSE. Therefore, an absolute reduction in the need for rescue medication is the true indicator of the effectiveness of the treatment. In fact, the marked relief from symptoms and freedom from breakthrough arthritic pain prompted many patients in the SLBSP group to continue treatment long after the trial was completed. However, the limitations of this study centered around the short trial duration, as it did not investigate the long-term effects of the drug on the disease.

It would be interesting to study the effect of the SLBSP on the radiological and clinical progression of OA after prolonged administration. Although, there was no clinically significant change in laboratory parameters due to oral administration of Boswellia, several minor side effects have been reported from oral consumption of *Boswellia*. Therefore, this contributed to the testing of a topical oily solution containing an extract rich in Boswellia acids in the treatment of Osteoarthritis of the knee. The results of this study represented the possibility that the topical solution of frankincense extract reduces the severity of pain and knee stiffness and improves the daily activity of patients. This work is considered the first to evaluate a *Boswellia* extract as a topical form in patients with OA (Afsaneh Mohsenzadeh *et al.,* 2023). However, the main limitations of this study were the small sample size and the short duration of the intervention. Therefore, a topical treatment using *Boswellia* should be tested for a longer period and for a larger number of participants to clarify its effectiveness more accurately.

## 5. Conclusion

The results of this systematic review suggest that *Boswellia* extract combinations could be a valuable addition to drug treatment regimens for knee OA by reducing pain, improving function, and reducing the risk of adverse events. Future research should consist of larger, higher-quality randomized controlled trials that specifically examine the role of *Boswellia* formulations as adjunctive therapies for NSAID-dependent knee osteoarthritis patients and should focus on their efficacy and safety over a longer period in patients with osteoarthritis of the knee.

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## Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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