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Original Research Article

Efficacy of bromelain and curcumin combination as an add-on therapy in outpatients with knee osteoarthritis: a randomized clinical trial

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Abstract

Objective: Knee osteoarthritis (KOA), a prevalent degenerative joint disease, often requires long-term management with nonsteroidal anti-inflammatory drugs (NSAIDs) which carry adverse effects. Bromelain and curcumin, with anti-inflammatory and analgesic properties, offer a safer adjunct treatment. This study investigates the efficacy of a bromelain-curcumin supplement combined with NSAID therapy in KOA patients.

Materials and Methods: A 4-week randomized controlled trial enrolled 60 KOA outpatients divided into three groups via block randomization: First group received celecoxib (200 mg once daily) plus bromelain (200 mg)-curcumin (300 mg) (twice daily) (Cele L + Sup), second group received celecoxib (200 mg once daily) (Cele L), and the last group received celecoxib (200 mg twice daily) (Cele H). Outcomes were assessed using WOMAC and Visual Analog Scale (VAS) scores at baseline, week 2, and week 4. The trial was registered in the Iranian Registry of Clinical Trials (IRCT20230629058615N4).

Results: Group Cele L + Sup showed greater reductions in pain (VAS) and functional improvement (WOMAC) versus Cele L ($p<0.05$). Cele L + Sup also showed comparable efficacy to Cele H, indicating enhanced symptom relief with lower NSAID use. No severe adverse events were reported, showing good tolerability.

Conclusion: Bromelain-curcumin with celecoxib improved KOA symptoms and function within 4 weeks, potentially reducing reliance on higher NSAID doses and associated risks. These findings support the bromelain-curcumin promise as a complementary therapy, though larger, longer-term studies with biomarker analysis are needed to confirm clinical benefits and mechanisms.

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Introduction

Osteoarthritis (OA) of the knee is a prevalent degenerative joint disease characterized by pain, stiffness, and reduced mobility, significantly impacting patients' quality of life. The pathophysiology of OA involves the progressive breakdown of articular cartilage, subchondral bone remodeling, synovial inflammation, and osteophyte formation. This degenerative process is driven by an imbalance between cartilage synthesis and degradation, mediated by pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which promote the production of matrix-degrading enzymes like matrix metalloproteinases (MMPs) and aggrecanases. Additionally, mechanical stress and oxidative stress further exacerbate cartilage damage and joint dysfunction (Yunus et al. 2020). As the global population ages, the burden of knee OA continues to rise, necessitating effective and safe therapeutic interventions (Neogi 2013). Conventional treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics, often provide symptomatic relief but are associated with potential adverse effects, particularly with long-term use (Scott et al. 2000). For instance, celecoxib, a selective cyclooxygenase 2 (COX-2) inhibitor, while effective in reducing inflammation and pain, has been linked to cardiovascular risks, gastrointestinal complications, and renal impairment (Brater 2002; Gong et al. 2012). Consequently, there is growing interest in exploring natural compounds with anti-inflammatory and analgesic properties as adjunctive or alternative therapies (Gandhi et al. 2022). The fact that these compounds exhibit anti-inflammatory properties could highlight their potential effects in managing knee osteoarthritis (KOA).

Bromelain, a proteolytic enzyme derived from pineapple stems, and curcumin, a polyphenolic compound found in turmeric, have garnered attention for their potential therapeutic benefits in inflammatory conditions (Rathnavelu et al. 2016; Sharifi-Rad et al. 2020). Both agents exhibit anti-inflammatory, antioxidant, and immunomodulatory properties, making them promising candidates for managing KOA symptoms and some other conditions such as treating acne scars (Hsiao et al. 2021; Savadjani et al. 2023; Shamsnia et al. 2023; Shojaan et al. 2024). Research conducted in both laboratory and clinical settings has shown that bromelain possesses fibrinolytic, anti-edema, anti-thrombotic, and anti-inflammatory effects (Pavan et al. 2012). It produces anti-inflammatory effects by reducing the production of prostaglandin E2 (PGE2) and COX-2 (Bhui et al. 2009). Curcumin interacts with Toll-like receptors (TLRs) and modulates downstream signaling pathways, including nuclear factor kappa-B (NF-κB), mitogen-activated protein kinases (MAPK), and activator protein 1 (AP-1) (Peng et al. 2021). However, despite their widespread use in complementary medicine, robust clinical evidence supporting their efficacy remains limited.

This research assesses how effective bromelain and curcumin supplements are for outpatients with KOA. It focuses on providing strong evidence about their ability to reduce pain, improve joint function, and enhance life quality. The results could help create safer treatments for this condition. However, there are not enough well-structured randomized controlled trials to fully evaluate their therapeutic potential, and existing studies have limitations like small groups and short durations.

Materials and Methods

Study design

This study was a double-blind, randomized controlled trial conducted at a medical clinic in Tehran, Iran. It was conducted and documented in strict adherence to Consolidated Standards of Reporting Trials (CONSORT) guidelines to

maintain methodological robustness and reporting transparency. The study's protocol received approval from the ethics committee of the Iran University of Medical Sciences (Ethic code: IR.IUMS.REC.1402.1029), and the clinical trial was registered in the Iranian Registry of Clinical Trials (IRCT code: IRCT20230629058615N4).

Participants

Eligible participants were adult patients aged 18 years or older diagnosed with KOA based on radiographic evidence (Kellgren-Lawrence grade ≥ 2) and clinical symptoms consistent with the American College of Rheumatology (ACR) criteria (Altman et al. 1991). Exclusion criteria included hypersensitivity to pineapple or curcumin, concurrent use of anticoagulants, severe hepatic or renal impairment, pregnancy, lactation, or any condition that could interfere with the study protocol (Figure 1).

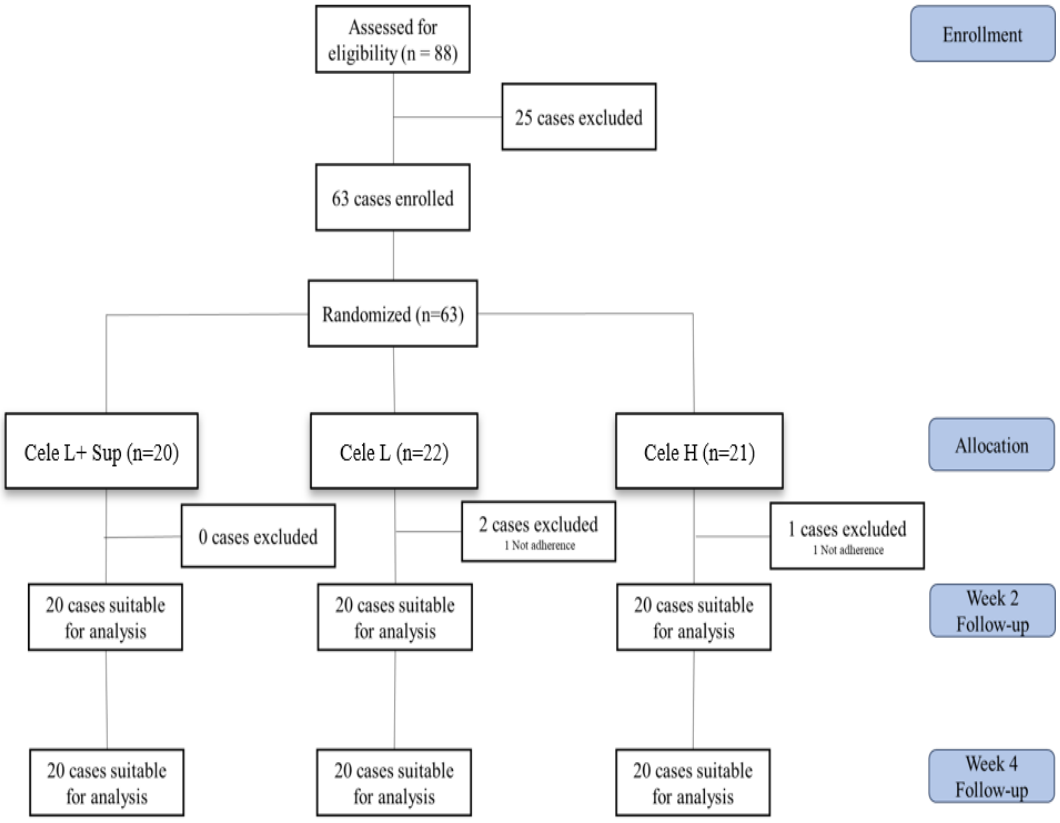

Figure 1. CONSORT flowchart

Randomization and blinding

Participants were randomly assigned to one of three intervention groups using a computer-generated block randomization sequence to ensure balanced allocation. The randomization list was prepared by an independent statistician and concealed from the investigators and participants to maintain blinding. The study was a double-blind randomized controlled trial (RCT), meaning participants and investigators were unaware of group assignments.

Interventions

The three intervention groups were as follows:

Group A (Cele L + Sup) received celecoxib 200 mg once daily, combined with bromelain-curcumin supplementation (produced by Salamat Parmoon Amin Company, Tehran, Iran, containing 150 mg

of bromelain plus 300 mg of curcuminoids at 95% concentration) twice daily.

Group B (Cele L) was administered celecoxib 200 mg once daily.

Group C (Cele H) was given celecoxib 200 mg twice daily.

The intervention lasted four weeks, during which participants were given standardized dosages of the study medications and supplements. Compliance was monitored through pill counts and patient diaries, and any deviations were recorded.

Study outcomes

Clinical assessments were conducted at baseline, at the two-week midpoint, and at the end of the four-week intervention period. The primary endpoint was pain intensity, measured using the VAS (0-10). Secondary endpoints included joint function and stiffness, which were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Safety parameters, such as gastrointestinal symptoms and other adverse events, were recorded and evaluated.

Sample size calculation

The sample size for this study was determined using Cochran's formula for finite populations. Based on this calculation, the minimum required sample size was initially determined to be 55 participants. To account for potential non-response or attrition, thereby enhancing the robustness and reliability of the data, the final sample size was increased to 60 participants.

Statistical analysis

The statistical analysis was conducted using PRISM and SPSS, with significance set at $p<0.05$. A two-way repeated-measures ANOVA assessed the effects of time (baseline, week 2, and week 4) and group (group Cele L + Sup, group Cele L, and group Cele H), and their interaction (time × group), on pain intensity (VAS) and WOMAC subgroup scores. Post-hoc tests with Bonferroni correction were performed to identify specific group differences when significant effects were found. Assumptions were checked using Mauchly's test and Levene's test, with Greenhouse-Geisser corrections applied if needed. Safety parameters were analyzed descriptively, and missing data were handled using an intention-to-treat approach with the last observation carried forward (LOCF).

Results

Study participants

The study included 60 patients divided into three groups (Group Cele L + Sup, Group Cele L, and Group Cele H), with 20 patients in each group. Most participants were female (95%), with a mean age of 56.07 years (±5.68). The mean weight and height of the participants were 75.97 kg (±7.28) and 166.08 cm (±4.11), respectively. The mean BMI was 27.57 (±2.31). A history of cardiovascular disease was reported in 58.3% of the participants, while 30% had a history of diabetes mellitus (Table 1).

Subgroup analysis of the WOMAC score

All groups experienced significant improvement in stiffness (Figure 2a), pain (Figure 2b), and functional limitations (Figure 2c) over the four-week study period. Generally, group Cele H demonstrated the greatest improvement in symptoms compared to other groups. When comparing group Cele L + Sup and group Cele L, no statistically significant differences were observed at any individual time point across the WOMAC subscales (pain, stiffness, and functional limitations). However, each group individually showed significant reductions in symptoms from baseline to weeks two and four (all $p < 0.0001$) (Table 2).

Total WOMAC score

All three groups showed significant improvement in total WOMAC scores over the study period (Figure 2d). Initially, group Cele L + Sup had the highest severity (49.55 ± 11.56), and group Cele L had the lowest (35.40 ± 11.52). By week two, each group experienced significant reductions, and this trend continued through week four. While group Cele H demonstrated the greatest overall improvement, a direct comparison between the other two groups revealed that group Cele L + Sup had a significantly greater reduction in total WOMAC scores than group Cele L at both week two (−7.15 ± 2.94 vs. −4.80 ± 1.94, p = 0.0025) and week four (−16.05 ± 5.95 vs. −9.55 ± 3.05, p = 0.0006)(Figure 2e). This suggests that the treatment given to group Cele L + Sup was more effective in improving osteoarthritis symptoms compared to that in group Cele L (Table 3).

Pain VAS score

The VAS scores for pain showed significant improvement across all groups from baseline to week 4. Initially, pain levels were similar among groups. At the two-week follow-up, pain scores decreased notably in all groups, with group Cele H showing the most pronounced improvement. However, when specifically comparing the other two groups, group Cele L + Sup exhibited a greater reduction in pain compared to group Cele L at week 2 (3.75 ± 1.21 vs. 3.25 ± 1.45). By week 4, this trend continued, with group Cele L + Sup (2.2 ± 1.20) showing slightly better pain relief than group Cele L (2.4 ± 1.27), though the difference was not statistically significant. These results indicate that while all treatments effectively reduced pain, group Cele L + Sup experienced marginally greater pain relief than group Cele L (Table 3).

Table 1. Demographic characterization

Variable	Cele L + Sup (n=20)	Cele L (n=20)	Cele H (n=20)	Total (n=60)
Age (years old)	56.65 (±5.51)	56.40 (±6.76)	55.15 (±4.77)	56.07 (±5.68)
Weight (kg)	76.81 (±6.33)	75.79 (±9.57)	75.30 (±5.64)	75.97 (±7.28)
Height (cm)	167.38 (±3.29)	165.20 (±5.71)	165.66 (±2.52)	166.08 (±4.11)
BMI	27.51 (±2.16)	27.71 (±2.59)	27.47 (±2.26)	27.57 (±2.31)
Female (%)	95.00%	90.00%	100.00%	95.00%
Cardiovascular History (%)	65.00%	70.00%	40.00%	58.30%
Diabetes Mellitus (%)	35.00%	30.00%	25.00%	30.00%

Cele L + Sup: celecoxib (200 mg/day) plus bromelain-curcumin supplements (twice daily). Cele L: celecoxib (200 mg/day). Cele H: celecoxib (200 mg twice daily)

Table 2. Comparison of stiffness, functionality, and pain scores across treatment groups at baseline, week 2, and week 4

Parameter	Time point	Cele L + Sup	Cele L	Cele H	p value§
Stiffness	Baseline	4.6 ± 1.18	3.5 ± 1.82	4.4 ± 2.06	ns
	Week 2	3.3 ± 0.92†	2.6 ± 1.67†	2.2 ± 1.82†	ns
	Week 4	1.55 ± 0.89‡	1.85 ± 1.27‡	1.15 ± 1.04‡	ns
Functionality	Baseline	33.5 ± 7.49	22.6 ± 7.99	28.2 ± 9.00	***
	Week 2	29.3 ± 7.25†	20.0 ± 7.43†	17.7 ± 7.81†	***
	Week 4	24.5 ± 6.82‡	17.1 ± 6.83‡	13.6 ± 5.62‡	**
Pain	Baseline	11.4 ± 3.20	9.3 ± 3.52	10.5 ± 2.95	ns
	Week 2	9.7 ± 2.82†	8.8 ± 3.03†	6.4 ± 2.04†	ns
	Week 4	7.4 ± 2.39‡	6.8 ± 2.79‡	4.7 ± 1.65‡	ns

† indicates differences between week 2 and baseline with $p < 0.001$. ‡ indicates differences between week 4 and baseline with $p < 0.001$. § Comparison between groups Cele + Sup and Cele L at baseline, and after 2 and 4 weeks. $p<0.05$ *$p<0.01$ **$p<0.001$ ***, *ns = not significant*. Cele L + Sup = celecoxib 200 mg/day + bromelain-curcumin supplement (twice daily). Cele L = celecoxib 200 mg/day. Cele H = celecoxib 200 mg twice daily

Table 3. Comparison of WOMAC scores, WOMAC reduction, and VAS (pain scores) across treatment groups at baseline, week 2, and week 4

Parameter	Time point	Cele L + Sup	Cele L	Cele H	p value[§]
Total WOMAC	Baseline	49.5 ± 11.56	35.4 ± 11.52	43.1 ± 11.95	**
	Week 2	42.4 ± 10.26[†]	30.6 ± 10.39[†]	26.3 ± 9.46[†]	**
	Week 4	33.5 ± 8.61[‡]	25.9 ± 9.44[‡]	19.5 ± 6.79[‡]	*
WOMAC reduction	Week 2-0	−7.15 ± 2.94	−4.8 ± 1.94	−16.8 ± 4.57	ns
	Week 4-0	−16.05 ± 5.95	−9.55 ± 3.05	−23.65 ± 6.02	****
VAS	Baseline	5.9 ± 1.48	4.95 ± 1.40	5.65 ± 1.18	ns
	Week 2	3.75 ± 1.21[†]	3.25 ± 1.45[†]	2.5 ± 0.95[†]	ns
	Week 4	2.2 ± 1.20[‡]	2.4 ± 1.27[‡]	1.3 ± 0.86[‡]	ns

† indicates differences between week 2 and baseline (week 0) with p<0.001. ‡ indicates differences between week 4 and baseline (week 0) with p<0.001. § Comparison between groups Cele L + Sup and Cele L at each time point. p<0.05 *p<0.01 **p<0.001 ***p<0.0001 ****, *ns = not significant*. Cele L + Sup = celecoxib 200 mg/day + bromelain-curcumin supplement (twice daily). Cele L = celecoxib 200 mg/day. Cele H = celecoxib 200 mg twice daily. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = Visual Analogue Scale

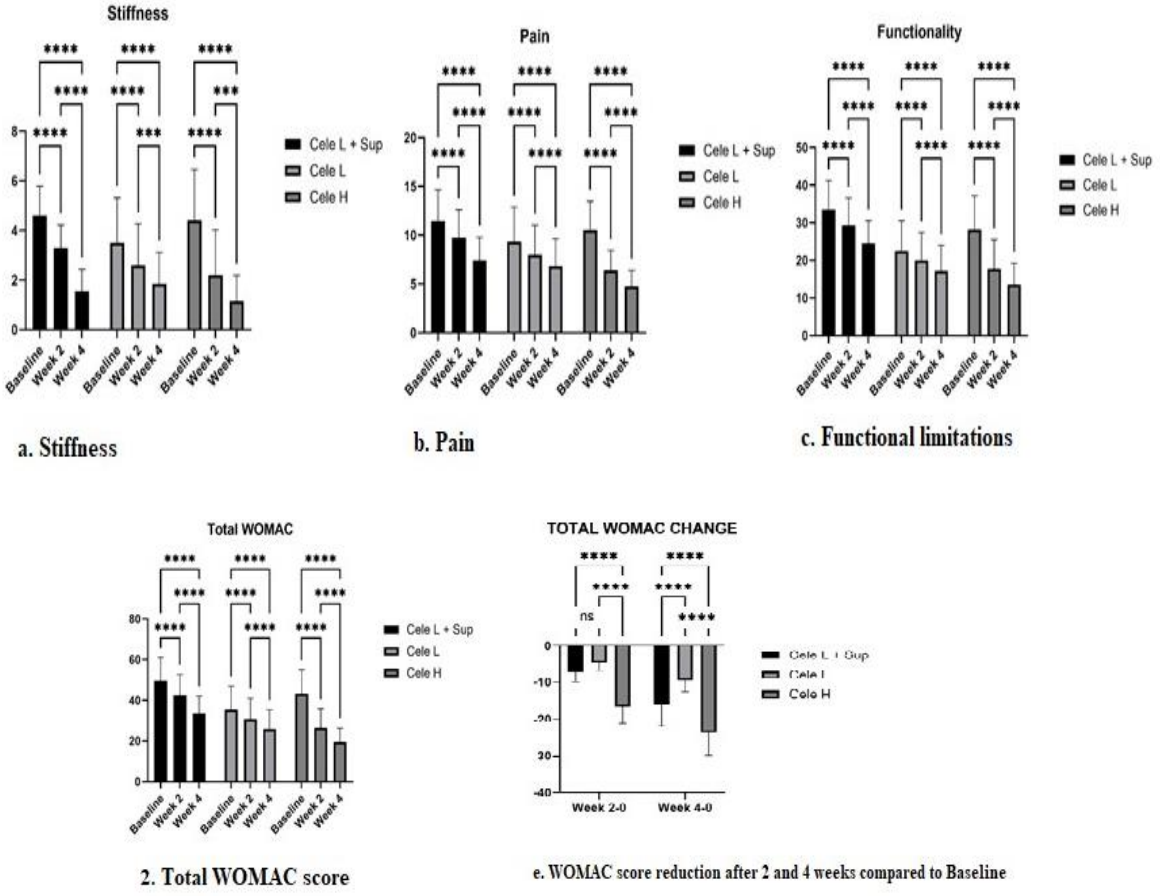

Figure 2. WOMAC score reduction after 2 and 4 weeks compared to baseline

Discussion

The present study evaluated the effect of adding a bromelain-curcumin supplement to a standard NSAID regimen (celecoxib) in managing KOA symptoms. The findings suggest that combining the supplement with celecoxib leads to greater symptom improvement than celecoxib alone, particularly in terms of pain reduction and knee function. While all treatment groups showed statistically

significant reductions in KOA symptoms based on the total WOMAC score, the highest improvement was observed in the group receiving a higher celecoxib dose (Cele H). Notably, the supplement group (Cele L + Sup) achieved greater symptom relief than the low-dose celecoxib group (Cele L), despite starting with a higher initial pain score. These results align with prior research emphasizing the anti-inflammatory benefits of curcumin and bromelain, reinforcing their potential role in OA management.

A study published by Quarta et al. (2022) assessed the anti-inflammatory and anti-arthritic potential of the dietary supplement containing *Boswellia serrata*, curcuminoids from *Curcuma longa*, and bromelain using various *in vitro* methods such as cell cultures, cell stimulation, biochemical measurements, molecular analyses, and statistical evaluations. This supplement significantly reduced inflammatory cytokines like interleukin 6 (IL-6) and TNF-α, which play crucial roles in inflammation and osteoarthritis progression. The expression of inflammatory genes such as inducible nitric oxide synthase (iNOS) and COX-2, as well as cartilage degradation-related genes (MMPs and a disintegrin and metalloproteinase with thrombospondin motif (ADAMTS)), was significantly reduced following treatment with this supplement, highlighting its potential in protecting cartilage tissue and mitigating osteoarthritis-related damage (Quarta et al. 2022). The current study supports these findings by demonstrating the clinical effectiveness of bromelain-curcumin supplementation in reducing KOA symptoms, further validating the anti-inflammatory properties of these compounds in a human population.

Similarly, a 2020 study by Italiano et al. examined the effects of a dietary supplement containing *Boswellia serrata* and bromelain on the quality of life of osteoarthritis patients. The study involved 49 participants (6 men and 43 women), aged 23 to 92 years (mean age 63.24 years), in a non-randomized, open-label interventional pilot study. WOMAC scores were used to evaluate pain, stiffness, and physical function. Pain intensity was measured using the VAS, showing a significant reduction after 60 days of supplementation, consistent with our study's findings. These studies suggest that a combination of *Boswellia serrata* and bromelain may improve osteoarthritis symptoms (Italiano et al. 2020). Likewise, our study found that after 28 days, supplementation alongside NSAIDs led to a greater reduction in WOMAC scores than low-dose celecoxib alone; however, this study had a shorter duration of intervention.

In another study conducted by Gupte et al. (2019), curcumin formulated using solid lipid curcumin particles (SLCP) technology was evaluated in KOA patients. Among the 50 participants, 25 in the ibuprofen group and 17 in the SLCP group completed the study with significant improvements in VAS and WOMAC scores, suggesting the comparable efficacy of SLCP to ibuprofen in pain reduction. The study found no significant difference between curcumin (80 mg twice daily) and ibuprofen (400 mg twice daily), supporting findings from our research (Gupte et al. 2019). Our study similarly observed that curcumin supplementation contributed to symptom relief when combined with NSAIDs, reinforcing curcumin's potential as an alternative or adjunct treatment in KOA management.

A 2016 study by Kasemsuk et al. assessed the effects of a 16-week bromelain treatment in patients with mild to moderate KOA. Forty patients were randomly assigned to two groups: one receiving 500 mg of bromelain daily and the other receiving 100 mg of diclofenac daily. No significant difference in total WOMAC and pain subscale reduction was observed between the two groups after four weeks. Assessments at baseline and at weeks 4, 8, 12, and 16 revealed overall WOMAC improvements in both groups by week 4.

However, two patients in the diclofenac group discontinued treatment due to adverse effects. While bromelain showed no difference in symptom reduction compared to diclofenac after four weeks, it demonstrated continued improvements in subgroups by week 16. These findings highlight the benefits of bromelain and curcumin in reducing osteoarthritis symptoms compared to NSAIDs. Moreover, bromelain was found to be safe and effective for up to 16 weeks, whereas diclofenac led to adverse effects, causing patient dropout. Based on these findings, our study also observed that after four weeks, supplementation led to a greater reduction in pain scores than an equivalent dose of NSAIDs alone. The difference was statistically significant at both weeks 2 and 4. In the total WOMAC subscales (pain, stiffness, and functional limitation), no significant difference was found between groups Cele L + Sup and Cele L, although at week 4, the scores in group Cele L + Sup were lower than in group Cele L (Kasemsuk et al. 2016). Similar to Kasemsuk et al. study, continued supplementation may lead to further improvements over time compared to NSAIDs alone.

Overall, comparisons with previous studies suggest that combining curcumin and bromelain with NSAIDs such as celecoxib may enhance WOMAC score improvements and pain reduction in osteoarthritis patients. Moreover, extending treatment duration could yield even more satisfactory outcomes which future studies should explore. Our findings align with previous research demonstrating the clinical efficacy of curcumin and bromelain in OA management while providing new insights into their benefits when used alongside NSAIDs.

Conversely, a 12-week, a double-blind, placebo-controlled randomized clinical trial by Brien et al. (2006) investigated bromelain as an adjunct therapy in patients with moderate-to-severe KOA. Participants received either 800 mg of bromelain daily (two 400 mg tablets) or a placebo. They were allowed to use NSAIDs as needed, with usage carefully recorded. In this study, 47 patients were randomized, with 31 completing the trial (14 in the bromelain group and 17 in the placebo group). No significant differences were observed between groups for the primary outcome (coefficient 11.16, $p = 0.27$, 95% CI: -8.86 to 31.18) or WOMAC subscales. Both groups showed clinically relevant improvements only in the WOMAC disability subscale. Adverse events were generally mild. This study suggests that bromelain is ineffective as an adjunct therapy for moderate-to-severe KOA. However, the enzymatic activity of bromelain used (measured by Gelatin Digestion Unit (GDU)) was not assessed, and the number and dose of NSAIDs used were not analyzed between groups. Future trials should account for NSAID consumption to better assess bromelain's efficacy in osteoarthritis symptom reduction (Brien et al. 2006). Unlike Brien et al. study, our research demonstrated significant improvements with bromelain-curcumin supplementation, suggesting that formulation, dosage, and combination with NSAIDs may influence treatment efficacy. These findings highlight the importance of optimizing supplement formulations to maximize their therapeutic effects.

The primary limitations of this study are its short duration and small sample size, which may limit the generalizability of the findings. A longer follow-up period could provide additional insights into the sustained efficacy of bromelain-curcumin supplementation. Moreover, the baseline imbalance in participants' scores can be considered a limitation of this study. Therefore, we analyzed change-from-baseline scores to reduce the effect of this imbalance in the results of the study. Furthermore, assessing inflammatory biomarkers such as C-reactive protein (CRP) and IL-6 could help elucidate the underlying mechanisms of action. While these biomarkers would have enriched mechanistic insights, their analysis was

precluded by budget constraints and ethical considerations (additional invasive procedures could reduce patient compliance in this RCT).

Studies show that a combination therapy with a supplement containing bromelain and curcumin, along with celecoxib capsules, can reduce pain, stiffness, and functional limitations in KOA patients. The addition of bromelain-curcumin to standard therapy may reduce reliance on NSAIDs like celecoxib, minimizing the need for higher doses and thereby lowering the risk of dose-dependent adverse effects. The bromelain-curcumin supplement, when used alongside 200 mg of daily celecoxib, leads to a significant reduction in osteoarthritis symptoms within four weeks compared to the equivalent dose of the analgesic alone. The supplement's role in reducing the need for analgesics and mitigating side effects is highlighted. However, longer studies are needed to fully demonstrate the efficacy in these patients.

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Conflicts of interest

Medicines and placebos were prepared by Salamat Parmoon Amin Company. None of the authors received financial or research support for this article, and do not have personal financial interests or shares in the company, or personal and professional relationships with this company. None of the authors are members of the editorial board or reviewer of this journal. There are no conflicts of interest.

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Ethical Considerations

All patients were included in this clinical trial study after a detailed explanation of the project and obtaining informed consent.

Code of Ethics

This study was approved under the ethical approval code IR.IUMS.REC.1402.1029.

Authors' Contributions

Mobina Tajdari, Hosein Kalvandi, Kamyab Andarzbakhsh: data assessment and manuscript preparation, Pooya Norouzi: following study design, data collection, and analysis. Amir Rezazadeh, Parastoo Mirzabeigi, Behzad Khanmohammadi: study design, supervision, and critical revision of manuscript.

Clinical Trial Registration Code

IRCT20230629058615N4

Informed Consent

Written informed consent was obtained from all participants.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author(s) used ChatGPT in order to refine language clarity. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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