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Review Article

The effects of bromelain on osteoarthritis symptoms: A systematic review

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Abstract

Background and aims: Osteoarthritis (OA) is the most common skeletal and excruciating disease worldwide. This study aimed to investigate bromelain's effect and underlying mechanism on OA symptoms.

Methods: This systematic review was designed according to the PRISMA guidelines. An extensive search was undertaken in various databases, including PubMed, Web of Science, EMBASE, and Scopus. Finally, 14 articles were retrieved considering the inclusion and exclusion criteria of the study. The desired data were extracted and entered into an Excel file, and the outcomes of the studies underwent investigation.

Results: Bromelain downregulates inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin 6 (IL-6), IL-8, IL-1β, and interferon γ expression in synovial fibroblasts. In addition, bromelain inserts analgesic effects by decreasing vascular permeability to bradykinin and inhabitation its generation. Bromelain counteracts by increasing the levels of TNF-α, IL-1β, inducible nitric oxide synthase (iONS) levels, and lipid peroxidation while reducing those of superoxide dismutase, catalase, and prolidase. Another main antinociceptive effect property of bromelain is associated with its anti-inflammatory effect by relieving neuroinflammation and synovial membrane inflammation.

Conclusion: Bromelain indicated good therapeutic effects on reducing OA symptoms due to its anti-inflammatory and antioxidant effects. Although no specific bromelain-related side effects were not reported in the included studies, it is recommended that more laboratory studies should be conducted with different doses and appropriate methodology.

Keywords: Bromelain, Osteoarthritis, Arthritis, Systematic review

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Introduction

Osteoarthritis (OA) is a serious and most common skeletal disease around the world (1). The number of elderly who are affected by OA is likely to increase in recent years due to obesity and unhealthy diet (2,3). This disease causes a wide range of various complications to premature mortality (1). Pain, loss of function (locomotor restriction), difficulty ambulation, falls, radiculopathies, joint stiffness, and malalignment are associated with the disease complications (4). The proportion of disease-adjusted life years and the years of life lost due to musculoskeletal disorders (especially OA) has increased in recent years (5,6). In addition, OA impairs health-related quality of life in affected patients (7) and imposes many direct and indirect costs on the healthcare system and societies (8).

OA-related treatments are focused on reducing the symptoms of the disease, especially the patient's pain (9). Due to the chronic nature of the disease, the prescription of drugs should be based on minimal dosage and maximum efficiency as possible, and precautions such as other underlying diseases of the patient should be taken into consideration. For example, in the prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, contraindications and precautions relating to cardiovascular and gastrointestinal should be observed in the patient (10). Accordingly, it is necessary to find new strategy treatment methods which have both lower complications and lower costs. Therefore, herbal treatments have great potential in the treatment of a wide range of diseases and sometimes have favorable effects as complementary treatments (11). Herbal treatments or their derivatives such as bromelain can be used in inflammatory diseases due to their high antioxidant and anti-inflammatory properties (12-16). Bromelain is a complex combination and the proteolytic enzyme derived from the stem or root of the pineapple plant (*Ananas comosus*) and contains multiple endopeptidases of thiol (17). Although some studies reported the anti-arthritic effects of bromelain (18,19), there are still doubts

and unclear aspects about its effectiveness and mechanism of action (20,21). Hence, this study sought to investigate the effects and mechanism of bromelain on OA symptoms.

Materials and Methods

Data sources and search strategy

This systematic review was designed and implemented according to the PRISMA guidelines (http://prisma-statement.org/prismastatement/Checklist.aspx). In the first step, a search was undertaken in various databases, including PubMed, Web of Science, EMBASE, and Scopus on September 1, 2022. For this purpose, various keywords such as ((“bromelin”) OR (“bromelain”) AND (“osteoarthritis”) OR (“osteoarthrosis”)), which were mainly taken from MeSH, were used to search for articles in the mentioned databases.

Study selection

Next, the articles found in the databases were imported into the EndNote X8 (8 November 2016, Thomson Reuters) software, and duplicate records were removed. All studies in terms of titles/abstracts identified in the mentioned databases were independently screened by two researchers. Based on the inclusion criteria of this systematic review, the clinical trial design studies that addressed the effect of bromelain on OA symptoms were included in the review. Lack of access to the full text of the publications, non-English studies, and studies on the pineapple extract were considered the exclusion criteria. After completing the systematic literature review and screening studies based on the inclusion and exclusion criteria, the full texts of all included studies were reviewed by two sets of researchers. If any conflict or disagreement erupted between the two investigators, it was resolved by discussing the issue.

The stages of screening results and the reasons for their exclusion according to the PRISMA 2020 flow diagram are shown in Figure 1.

Data extraction

After reviewing the publications, the obtained data were extracted and registered in Excel form, including the

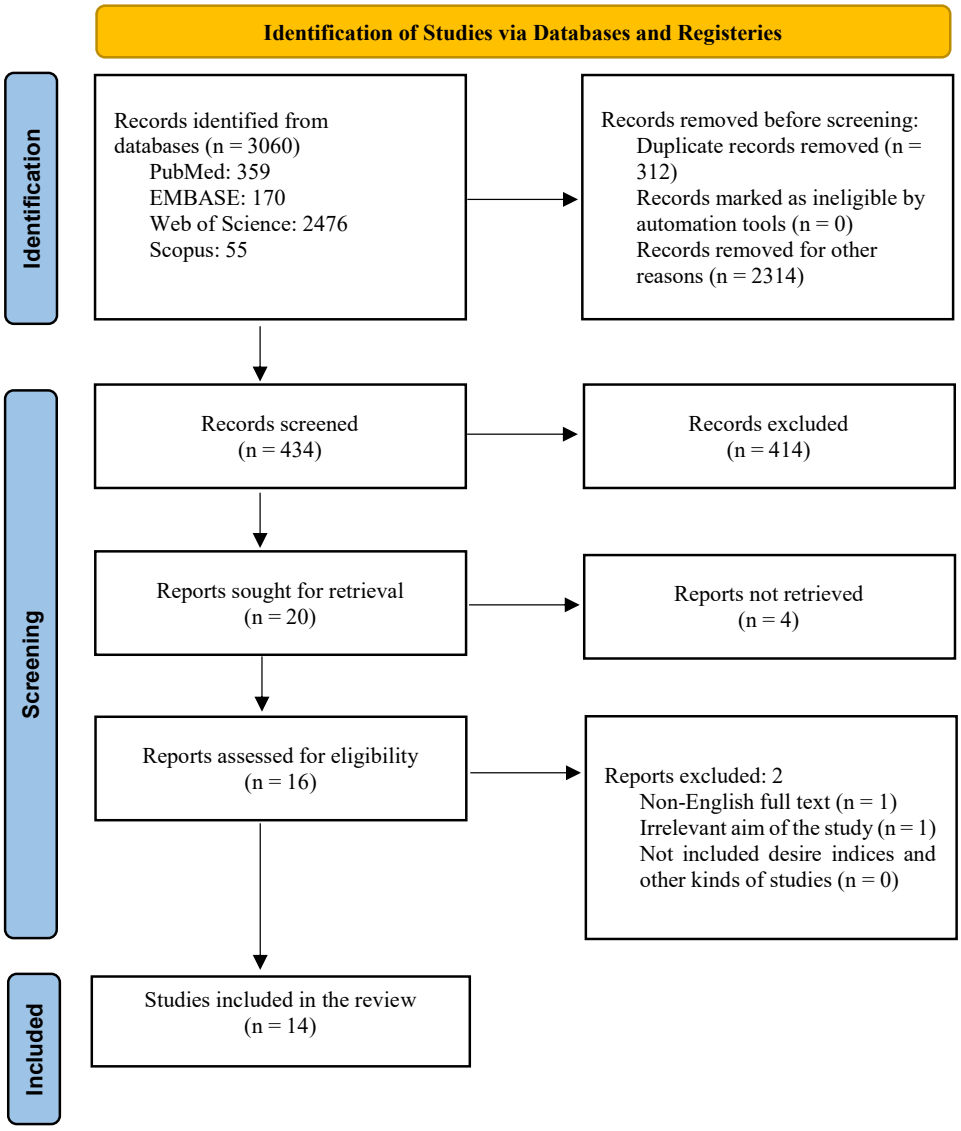

Figure 1. Flow Diagram for Including Studies in the Systematic Review

lead author's name, year of publication, country, sample size, involved joint, clinical approach and dosage, time of exposure, and outcomes. If the extracted information was not related to the purpose of the study, it was excluded from the study.

Results

Search results, study characteristics of selected studies

The PRISMA flowchart illustrated the included and excluded studies that were searched in the main databases (Figure 1). In general, about 3060 articles were retrieved in the initial search. Out of this number, about 312 articles in EndNote were removed due to duplication. Some other titles/abstracts were also excluded (n = 6) because of not having been published in English (n = 1, 22), being irrelevant to the aim of the study (n = 1, 23), and not being able to retrieve the full text (n = 4, 24-27).

Finally, 15 articles were selected for the final assessment (4,21,28-39). These articles mainly examined outcomes such as joint pain, joint stiffness, physical movements and joint range of motion, quality of life (especially in physical dimensions), and indicators related to joint health and abilities related to it. In addition, they were mainly conducted on the OA of the knee joint (Table 1).

By reviewing Table 1, bromelain, alone or in combination with other plant derivatives or active components, demonstrated good anti-inflammatory and analgesic effects, and even some studies represented no difference between its use and diclofenac in OA patients. In the meantime, none of the studies reported any specific complications related to its use. However, this issue can be investigated in higher doses.

The main underlying mechanism of bromelain on OA

Anti-inflammatory properties

Inflammation is involved in OA pathogenicity and is characterized as an innate immune response (complement pathway) to the disease (40). The destruction of cartilage and the inflammation of synovial cells cause the local production of inflammatory mediators. However, systemic pathways are also involved in this process, and inflammatory reactions that occur in joint tissues may occur outside the joint in peripheral blood leukocytes and the plasma of patients with OA (41).

Table 1. Characteristics of Selected Studies of the Effect of Bromelain on OA Symptoms

Lead Author	Year of Publication	Country	Sample Size	Involved Joint	Clinical Approach and Dosage	Duration	Main Outcomes
Klein (28)	2000	Germany	73	Knee	Oral Phlogenzym, 2 tablets 3 times a day	3 weeks	Lequesne index similarly improved in Phlogenzym and diclofenac groups
Singer (29)	2001	Germany	63	Knee	Oral Phlogenzym	3 weeks	The pain was equal in the diclofenac group, ↓Lequesne index
Tilwe (30)	2001	Germany	50	Knee	Oral Phlogenzym, 2-3 tablets	3 weeks	↓Pain, ↓joint tenderness, ↓swelling, and ↑range of movement
Walker (31)	2002	The UK	77	Knee	Oral bromelain administration, 200-400 mg/day	4 weeks	↑Total symptom score, ↓stiffness, ↑physical function, and ↑WOMAC
Akhtar (32)	2004	Germany	103	Knee	Oral Phlogenzym, tablets 3 times a day	6 weeks	↓Lequesne's Algofunctional Index, and the same effects as diclofenac
Brien (21)	2006	The UK	47	Knee	Oral bromelain administration, 800 mg/day	12 weeks	No statistically significant differences were observed between groups for the primary outcome, nor the WOMAC subscales or SF36
Klein (33)	2006	Germany	90	Hip	Oral Phlogenzym, 2 tablets/day	6 weeks	Non-inferiority was found in the WOMAC dimension stiffness, pain, and physical function to Lequesne's index
Conrozier (34)	2014	France	42	Knee	Two 650-mg AINAT capsules were applied 3 ×/d to patients with acute pain and 2 ×/d to patients with chronic pain	2 weeks and 2 months	↓Joint pain
Bolten (35)	2015	Germany	150	Knee	Wobenzym, 6 tablets (2 tablets, 3 times daily)	12 weeks	↓Joint pain, no difference was observed between Wobenzym and diclofenac in terms of WOMAC scores
Ishaque (36)	2015	Pakistan	60	Knee	Oral bromelain and papain 2 x BD	3 weeks	↓Joint pain and ↑physical function
Kasemsuk (37)	2016	Thailand	40	Knee	Oral bromelain, 500 mg/day	3-4 weeks	↓Joint pain, ↓stiffness, ↑physical function, the ↑physical component of SF-36, and ↑WOMAC
Jayachandran (38)	2017	India	30	TMJ	Oral bromelain, 90 mg/day	10 days	↓Joint pain
Gupta (39)	2020	India	30	TMJ	Oral bromelain, 90 mg/day twice daily	14 days	↓Joint pain, ↑chewing ability, ↑mouth opening, ↓joint noise, and ↓jerky mandibular movements
Naeem (4)	2020	Pakistan	40	Lumbar spine OA	Oral bromelain and Papain, 250 mg BD	6 weeks	↓Joint pain and Oswestry low back pain

Note. ↓: Reduced; ↑: Increase; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SF36: Short Form-36; AINAT: Composed of *Harpagophytum procumbens* (300 mg/capsule), *Curcuma longa* (200 mg/capsule), and bromelain (150 mg/capsule); Phlogenzym: Composed of bromelain 90 mg, trypsin 48 mg, and rutin × 3H20 100 mg); Wobenzym: Composed of 288 mg trypsin and 540 mg bromelain; OPERA: Composed of α-Lipoic acid 240 mg, Boswellia serrata 40 mg, Methylsulfonylmethane 200 mg, and Bromelain 20 mg TMJ; Temporomandibular joint; OA: Osteoarthritis.

Bromelain can downregulate inflammatory cytokine such as tumor necrosis factor (TNF)-α, interleukin 6 (IL-6), IL-8, IL-1β, and interferon γ (IFN-γ) expression in synovial fibroblasts through suppressing nuclear factor kappa B and mitogen-activated protein kinase signaling (18). Hence, it inhibits the excess production of cytokines. Studies revealed that the native form of bromelain exhibits no considerable activity on COX-2 and inducible nitric oxide synthase (iNOS) expression levels, although the studied compound seems to produce an inhibitory effect on the TNF-α-induced activity of COX-2, in which COX-2 activity was fully inhibited by bromelain (42). On the other hand, a trend was observed for iNOS inhibition in cells treated with digested bromelain. The enzyme contributes substantially to prostaglandin H synthesis, beginning from the arachidonic acid substrate, through two independent reactions (COX-2 and peroxidase) that go through a prostaglandin G2 intermediate (43). Two mediators that determine the immune response, including prostaglandin E2 and substance P, are reduced in the OA mouse model (44). Bromelain also modulates its expression by the transforming growth factor (TGF)-β, which is the main vital regulator of the inflammation of OA (45,46). Through its effect on CD44-mediated activation and CD25-mediated modulation of T lymphocytes activity, bromelain regulates neutrophils and reduces monocytic cytotoxicity, as well as inserting its immuno-modulatory activity through down-regulation of the immune system inhibitor (TGF-β) (47).

Antioxidant properties

There is a significant relationship between OA progression and oxidative stress (OS). The OS and disruption of pro-oxidant antioxidant balance and the biochemical pathways of the cartilage site can lead to increased production of reactive oxygen species (ROS) in OA cartilage and chondrocytes. Thus, supplementation with natural antioxidants inhibits the destruction of cartilage caused by lipid peroxidation and slows down the process of cartilage degradation (48). OS has a direct relationship with joint inflammatory processes and changes in the immune system. The levels of TNF-α and IL-1β, iONS levels, and lipid peroxidation increase, while superoxide dismutase (SOD), catalase, and prolidase decrease during OS. Due to increasing lipid peroxidation, the production of 4-hydroxynonenal increases as well. The basis for the inhabitation of expression of collagen II synthesis and its breakdown could be provided by increasing the 4-hydroxynonenal (49).

In vitro and *in vivo* studies provided evidence that plant antioxidants can be effectively used in the treatment of OA so that plant-derived antioxidants play an effective role in pain relief and knee function in OA (50,51). Some studies revealed that bromelain is a mixture of different peroxidases, phosphatases, thiol proteases, glycoproteins, cellulases, carbohydrates, glucosidase, and several protease inhibitors which determine its antioxidant properties (20,52,53). According to previous experimental studies, bromelain in the treatment of cancer, by inducing its antioxidant activity, inhibits the mechanisms that lead to the production of ROS in cancer cells and helps cancer cell apoptosis and tumor size reduction (16,54,55).

Analgesic properties

Pain is one of the symptoms and uncomfortable side effects of OA. A set of complete joint involvement, especially synovial inflammation, cartilage, and joint disruption, is involved in the occurrence of pain caused by the disease. Additionally, altered sensitivity and pressure on peripheral nerves inside the knee may cause persistent pain in OA patients (56). Some studies have shown that bromelain, due to its analgesic properties, can be used as a complementary or even alternative treatment (Equal analgesic effects with NSAIDs) and demonstrate positive results for pain relieving in OA patients (29,35). Bromelain causes sciatic and structural integrity changes in the nervous system (57). There is evidence that bromelain can reduce pain in patients by directly acting on pain mediators such as bradykinin (58). The antinociceptive effects of bromelain are also associated with retaining a neuronal electrolyte (Na^+, Ca^{2+}, K^+, and Cl^-) disturbance (46,59). Moreover, bromelain can relieve pain by reducing pro-inflammatory cytokines and oxidative agents in the joint site. In addition to controlling neuroinflammation and synovial membrane inflammation, bromelain reduces the pain associated with fibromyalgia or neoplastic pain (60). Inflammation is particularly insidious where the peripheral and central nervous systems are involved ('neuroinflammation'), playing an important role in the pathogenesis of acute and chronic pain (60). Afferent neurons, via various pro-inflammatory mediators such as serotonin, H^+, histamine, and cytokines, strengthen the function of the dorsal horn of the spinal cord (60,61). Therefore, by reducing local inflammation, bromelain reduces the pain of OA patients.

Discussion

This systematic review aimed to evaluate bromelain's effect and underlying mechanism on OA symptoms. Most of the reviewed studies showed that bromelain reduces the complications of OA by inducing its anti-inflammatory and antioxidant properties in the body. Moreover, there was no specific report of its serious side effects. Henrotin et al revealed that oral combination enzymes, composing of bromelain with trypsin, both proteolytic enzymes and plant flavonoid rutin, may have similar effects as NSAIDs and help reduce pain and inflammation in OA patients (62). Another review study investigating the anti-inflammatory and anti-cancer effects of bromelain reported that bromelain, by its anti-inflammatory effects, could be used as adjuvant therapy for chronic inflammatory diseases such as OA (47). Bradley found that bromelain-containing enzyme combination therapy could be as effective as diclofenac in the treatment of OA

symptoms (63). In this regard, Pavan et al concluded that bromelain has properties, including anti-inflammatory, antiedematous, fibrinolytic, and antithrombotic activities. Therefore, they could relieve pains associated with OA (53). According to a review study, oral enzyme combination (including bromelain), compared to NSAIDs, showed better efficiency on OA symptoms, indicating fewer side effects in the treatment process, and fewer changes in laboratory parameters (64). One of the limitations of the studies was the lack of investigation of the long-term effects of bromelain on OA and the lack of investigation of its different doses. Further, the lack of control of some confounding variables such as the use of other drugs and the weight of patients was obvious in some studies. The conducted studies also sometimes had a low sample size, and the patients were not followed up at different times. In the current study, although the search was not performed in all the databases. The detailed and comprehensive survey of the reviewed databases and the review of the studies included in the other reviews are the strengths of this study.

Conclusion

The results revealed that bromelain, having anti-inflammatory, antioxidant, and analgesic properties, can be effective in the treatment of OA-related complications such as joint pain, joint stiffness, and pain. In addition, bromelain could increase the range of physical motion of the joints in OA patients. Thus, it can be used as a safe and cheap adjutant treatment for OA. However, there is a need for more clinical trial studies to determine optimum efficacy, as well as experimental and dose-ranging studies to identify the complications and optimal dosage of bromelain on OA symptoms.

Authors' Contribution

Conceptualization: Shahin Asgari Savadjani.
Investigation: Armin Khaghani.
Methodology: Farshad Yadollahi.
Project Administration: Farshad Yadollahi.
Resources: Armin Khaghani.
Supervision: Armin Khaghani.
Visualization: Armin Khaghani.
Writing–original draft: Shahin Asgari Savadjani, Farshad Yadollahi.
Writing–review & editing: Armin Khaghani, Shahin Asgari Savadjani.

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Competing Interests

The authors declare that they have no conflict of interests.

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