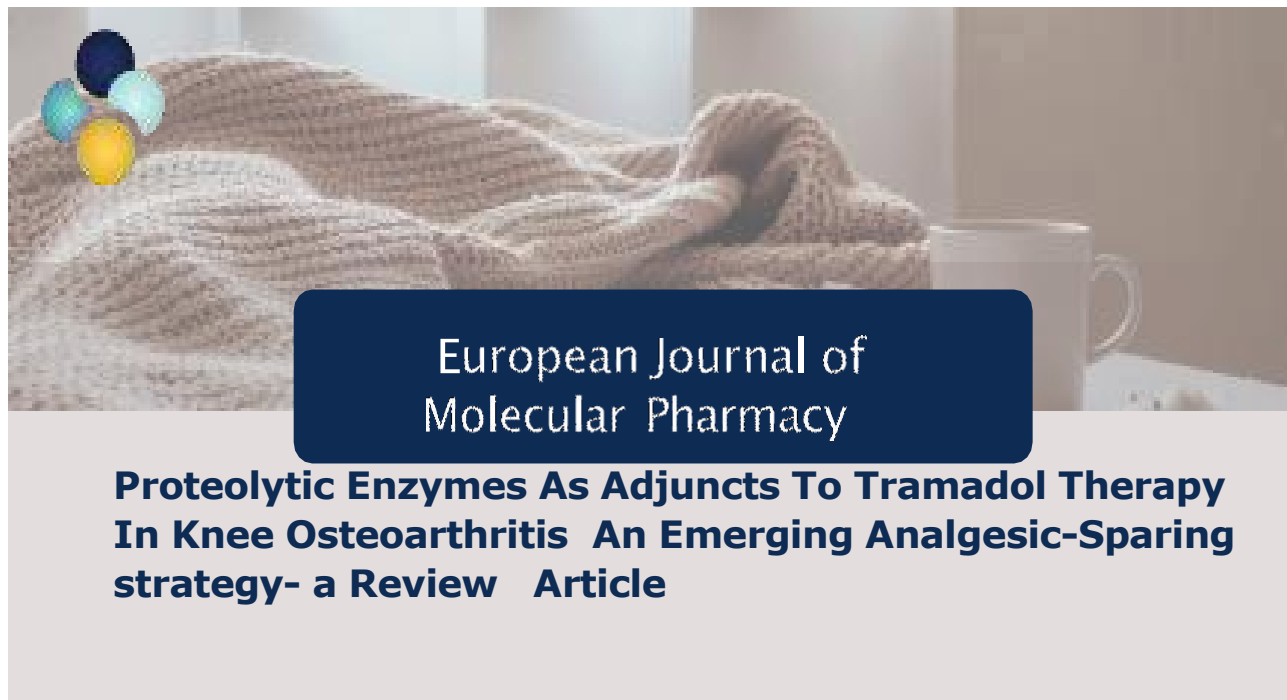




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Proteolytic Enzymes As Adjuncts To Tramadol Therapy In Knee Osteoarthritis An Emerging Analgesic-Sparing strategy- a Review Article

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Abstract

Knee osteoarthritis (KOA) is one of the most prevalent chronic musculoskeletal disorders and a major cause of pain, functional limitation, and reduced quality of life among the elderly population. Pharmacological management commonly includes nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioid analgesics such as Tramadol. Although tramadol is frequently prescribed for moderate to severe osteoarthritic pain, prolonged opioid use is associated with adverse effects, tolerance, dependence, and increased healthcare burden. Consequently, there is growing interest in analgesic-sparing strategies and opioid stewardship approaches that can optimize pain control while minimizing opioid exposure.

Proteolytic enzymes including bromelain, trypsin, chymotrypsin, and serratiopeptidase have emerged as potential adjunctive agents due to their anti-inflammatory, anti-edematous, and analgesic properties. These enzymes may reduce inflammatory mediators, improve tissue healing, and enhance symptomatic relief in osteoarthritis. Recent evidence suggests that combining proteolytic enzymes with tramadol-based therapy may improve pain management outcomes, reduce analgesic requirements, and enhance tolerability.

This review discusses the pathophysiology of knee osteoarthritis, the therapeutic role and limitations of tramadol, and the pharmacological basis of proteolytic enzyme therapy. Furthermore, it evaluates the current clinical evidence supporting the use of proteolytic enzymes as adjuncts to tramadol therapy and highlights their potential contribution to multimodal analgesia and opioid stewardship in osteoarthritis care.

Keywords: Knee osteoarthritis, Proteolytic enzymes, Tramadol, Analgesic sparing, Opioid, stewardship Multimodal analgesia

1. INTRODUCTION

Knee osteoarthritis (KOA) is one of the most common chronic degenerative joint disorders and a leading cause of pain and disability worldwide. It is characterized by progressive degeneration of articular cartilage, synovial inflammation, osteophyte formation, and subchondral bone remodeling, ultimately resulting in impaired joint function and reduced quality of life. The global prevalence of osteoarthritis has increased substantially due to aging populations, obesity, sedentary lifestyle, and increasing life expectancy. Among all joints affected, the knee joint is the most frequently involved weight-bearing joint, contributing significantly to physical disability and socioeconomic burden [1].

Chronic pain associated with knee osteoarthritis is a major clinical concern, often leading to reduced mobility, stiffness, sleep disturbances, psychological stress, and limitations in activities of daily living. Persistent pain and functional impairment can negatively affect occupational productivity and overall well-being, particularly among elderly individuals. In advanced stages, chronic osteoarthritis pain may become refractory to conventional treatment approaches, necessitating long-term pharmacological intervention [2].

Current pharmacological management of knee osteoarthritis primarily focuses on symptomatic relief and improvement of functional status. Commonly used medications include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical analgesics, intra-articular corticosteroids, and opioid analgesics such as tramadol. Tramadol is often prescribed

for moderate to severe osteoarthritic pain when first-line therapies fail or are contraindicated. Owing to its dual mechanism involving μ -opioid receptor agonism and inhibition of serotonin and norepinephrine reuptake, tramadol provides effective analgesia in chronic musculoskeletal pain conditions [3].

However, prolonged use of tramadol and other opioid analgesics is associated with several limitations including nausea, dizziness, constipation, sedation, dependence, tolerance, and risk of misuse. Increasing concerns regarding opioid-related adverse effects and the global opioid crisis have highlighted the importance of opioid stewardship and the development of analgesic-sparing strategies in chronic pain management [4]. Consequently, there is growing interest in adjunctive therapies that can enhance pain control while minimizing opioid exposure.

Proteolytic enzymes such as bromelain, trypsin, chymotrypsin, and serratiopeptidase have emerged as potential adjunctive agents in osteoarthritis management because of their anti-inflammatory, anti-edematous, and analgesic properties. These enzymes may modulate inflammatory mediators, improve tissue healing, and reduce pain severity, thereby potentially decreasing the requirement for opioid analgesics. The use of proteolytic enzymes as adjuncts to tramadol therapy may represent a promising multimodal analgesic approach aimed at improving therapeutic outcomes and promoting safer long-term pain management in knee osteoarthritis [5].

KNEE OSTEOARTHRITIS

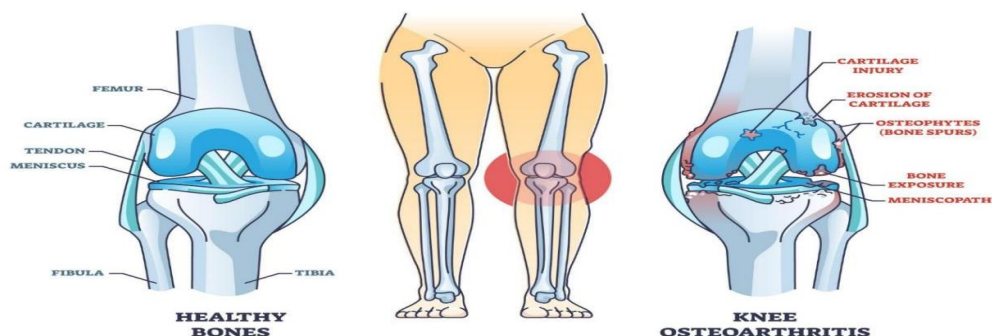


Figure 1: Anatomical representation of healthy and osteoarthritic knee joint

2. PATHOPHYSIOLOGY OF KNEE OSTEOARTHRITIS

Knee osteoarthritis (KOA) is a chronic, progressive, and multifactorial degenerative joint disorder characterized by structural and functional deterioration of the entire joint organ. It involves progressive cartilage degeneration, synovial inflammation, osteophyte formation, subchondral bone remodeling, ligament changes, and muscle weakness surrounding the joint. Mechanical stress, aging, obesity, genetic predisposition, metabolic abnormalities, and inflammatory mediators collectively contribute to disease initiation and progression [6].

Articular cartilage degeneration is a hallmark feature of KOA. Chondrocytes, the only cellular components of cartilage, maintain extracellular matrix homeostasis by balancing anabolic and catabolic activities. In osteoarthritis, this balance is disrupted, leading to increased degradation of collagen type II and proteoglycans by matrix metalloproteinases (MMPs) and aggrecanases. Progressive loss of cartilage elasticity and thickness results in joint space narrowing and impaired shock absorption [6].

Synovial inflammation plays a significant role in disease progression and symptom severity. Activated synovial cells release pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and prostaglandins, which amplify inflammatory responses and stimulate cartilage destruction. Inflammatory mediators also

promote recruitment of immune cells and increase production of reactive oxygen

species, further accelerating joint damage [7].

Subchondral bone remodeling is another important pathological feature in KOA. Increased bone turnover, sclerosis, microfractures, and cyst formation occur beneath the damaged cartilage. Osteophyte formation develops as a reparative response to chronic mechanical stress and contributes to joint stiffness and deformity. Alterations in bone architecture may further aggravate cartilage degeneration and pain sensitization [8].

Pain in osteoarthritis is complex and multifactorial. Since articular cartilage is aneural, pain primarily originates from surrounding structures including the synovium, subchondral bone, ligaments, periosteum, and joint capsule. Synovial inflammation, bone marrow lesions, mechanical stress, and nerve sensitization contribute to chronic pain perception. Peripheral sensitization caused by inflammatory mediators and central sensitization involving altered pain processing pathways may result in persistent and exaggerated pain responses in advanced disease [9].

Additionally, oxidative stress and low-grade chronic inflammation are increasingly recognized as important contributors to osteoarthritis progression. Excess production of reactive oxygen species can damage chondrocytes and extracellular matrix components, while metabolic inflammation associated with obesity further exacerbates joint degeneration [10].

PATHOPHYSIOLOGY OF KNEE OSTEOARTHRITIS

A multifactorial degenerative joint disease characterized by progressive cartilage destruction, synovial inflammation, subchondral bone remodeling, and osteophyte formation leading to pain and functional disability.

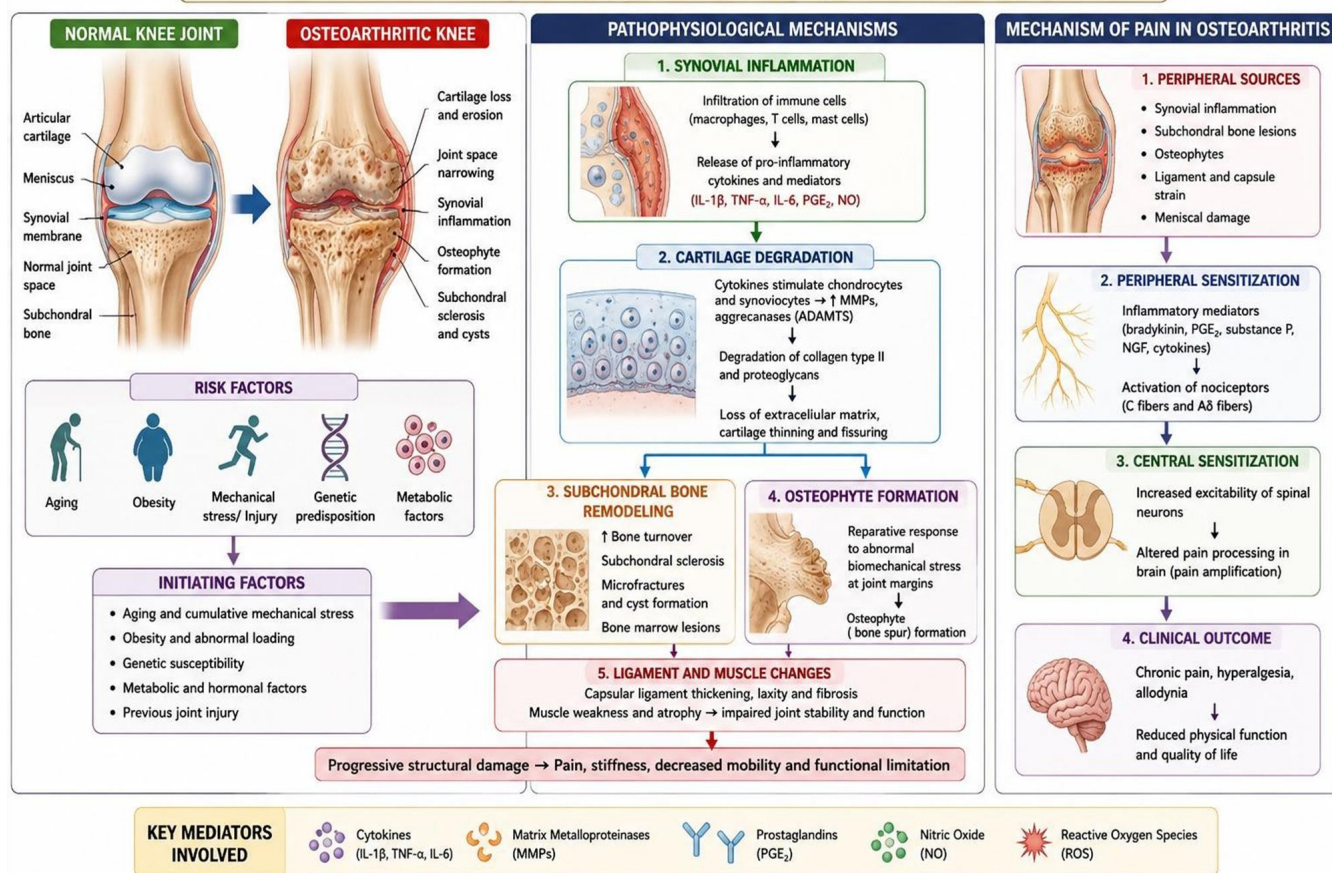


Figure 2: Pathophysiological Mechanism and Pain Development in Knee Osteoarthritis

Illustration of the risk factors, pathophysiology changes, and pain pathways involved in the progression of knee osteoarthritis leading to joint dysfunction and disability

3. CURRENT PHARMACOLOGICAL MANAGEMENT OF KNEE OSTEOARTHRITIS

Current pharmacological management of knee osteoarthritis (KOA) primarily focuses on alleviating pain, reducing inflammation, improving joint function, and enhancing quality of life. Since no definitive cure exists for osteoarthritis, treatment strategies are mainly symptomatic and are often individualized based on disease severity, patient comorbidities, and response to therapy [11].

Acetaminophen (paracetamol) is commonly used as an initial analgesic for mild osteoarthritic pain because of its relatively favourable safety profile. However, its analgesic efficacy is

modest, particularly in moderate-to-severe disease, and prolonged high-dose use may increase the risk of hepatotoxicity [9].

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain the cornerstone of pharmacological therapy because of their analgesic and anti-inflammatory properties. Commonly prescribed NSAIDs include ibuprofen, diclofenac, naproxen, celecoxib, and etoricoxib. Both oral and topical NSAIDs are widely used, with topical formulations preferred in elderly patients to minimize systemic adverse effects [10]. Despite their effectiveness, long-term NSAID use is associated with gastrointestinal ulceration, bleeding, cardiovascular complications, renal impairment, and hypertension, limiting their use in many patients [11].

Opioid analgesics, particularly tramadol, are considered when pain persists despite first-line therapies or when NSAIDs are contraindicated. Tramadol is preferred over stronger opioids because of its

comparatively lower abuse potential and dual mechanism of action involving μ -opioid receptor agonism and inhibition of serotonin and norepinephrine reuptake [12]. Nevertheless, chronic opioid therapy carries risks of nausea, constipation, dizziness, sedation, tolerance, dependence, and misuse.

Intra-articular therapies are also frequently employed for symptomatic relief. Corticosteroid injections provide rapid short-term reduction in inflammation and pain, especially during acute exacerbations. Hyaluronic acid injections aim to improve joint lubrication and viscoelasticity, although clinical benefits remain variable [10].

Adjuvant pharmacological therapies such as duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), have shown benefit in chronic osteoarthritis pain by modulating central pain pathways [13]. Nutraceuticals including glucosamine and chondroitin sulfate are also widely used, although evidence regarding their efficacy remains inconsistent.

Despite the availability of multiple therapeutic options, existing pharmacological treatments are associated with several limitations including incomplete pain relief, adverse drug reactions, poor long-term tolerability, and increased healthcare burden. These limitations have stimulated growing interest in multimodal analgesic strategies and safer adjunctive therapies that can reduce reliance on opioids and long-term NSAID use [14].

4. TRAMADOL IN KNEE OSTEOARTHRITIS

Tramadol is a centrally acting analgesic that exerts its effect through weak μ -opioid receptor agonism along with inhibition of serotonin and norepinephrine reuptake [12]. This dual mechanism contributes to its analgesic efficacy in both nociceptive and neuropathic pain components associated with osteoarthritis. It is commonly prescribed for moderate-to-severe knee osteoarthritis pain when conventional therapies fail or are contraindicated.

Tramadol is available in immediate-release and extended-release formulations, allowing flexibility in pain management. It is often considered a preferred weak opioid because it produces comparatively less respiratory

depression and lower abuse potential than stronger opioids such as morphine or oxycodone [13]. Clinical studies have demonstrated that tramadol can improve pain scores, physical mobility, sleep quality, and overall functional outcomes in patients with chronic osteoarthritis pain.

Despite these benefits, tramadol use is associated with several adverse effects including nausea, vomiting, constipation, dizziness, headache, sedation, dry mouth, and fatigue [13]. Elderly patients may be particularly susceptible to falls, confusion, and cognitive impairment associated with opioid therapy.

Long-term tramadol use may result in tolerance, physical dependence, withdrawal symptoms, and risk of misuse. Additionally, tramadol may increase the risk of serotonin syndrome and seizures, especially when combined with antidepressants or used in high doses [14]. These concerns have increased interest in multimodal analgesic approaches and adjunctive therapies aimed at reducing opioid exposure while maintaining adequate pain control.

5. CONCEPT OF ANALGESIC SPARING AND OPIOID STEWARDSHIP

Analgesic sparing refers to therapeutic strategies aimed at achieving effective pain control while reducing the dose, frequency, or duration of analgesic medications, particularly opioid agents. The primary objective of analgesic-sparing approaches is to minimize drug-related adverse effects without compromising pain relief or functional outcomes. Opioid stewardship, on the other hand, emphasizes the safe, rational, and evidence-based use of opioid medications to reduce risks of dependence, misuse, overdose, and long-term complications [15].

In chronic pain conditions such as knee osteoarthritis, prolonged opioid exposure can result in tolerance, physical dependence, opioid-induced hyperalgesia, and reduced quality of life. Therefore, current pain management guidelines increasingly recommend multimodal analgesic approaches that combine pharmacological and non-pharmacological therapies to optimize pain control while minimizing opioid burden [16].

Analgesic-sparing strategies may include the use of non-opioid medications, topical agents, physiotherapy, weight reduction, exercise therapy, cognitive behavioral therapy, and adjunctive anti-inflammatory agents. The addition of complementary therapies such as proteolytic enzymes may further enhance symptom control and reduce the need for escalating opioid doses.

Opioid stewardship has become particularly important in osteoarthritis management because the disease often requires long-term therapy. Safer adjunctive therapies capable of improving analgesic efficacy while reducing opioid exposure may contribute to better patient safety, improved tolerability, and reduced healthcare burden [17].

6. PROTEOLYTIC ENZYMES: OVERVIEW

Proteolytic enzymes, also known as proteases or proteinases, are biologically active compounds capable of hydrolyzing peptide bonds in proteins. These enzymes participate in various physiological processes including digestion, inflammation regulation, tissue remodeling, immune modulation, and wound healing. In recent years, proteolytic enzymes have gained attention as potential therapeutic agents in inflammatory and musculoskeletal disorders because of their anti-inflammatory and analgesic properties [17].

Commonly used therapeutic proteolytic enzymes include trypsin, chymotrypsin, bromelain, and serratiopeptidase. Trypsin and chymotrypsin are pancreatic enzymes that assist in protein breakdown and inflammation control. Bromelain is a plant-derived enzyme extracted mainly from the stem and fruit of pineapple (*Ananas comosus*), whereas serratiopeptidase is a protease produced by *Serratia* species bacteria [18].

These enzymes are available in oral tablet and capsule formulations, either alone or in combination with anti-inflammatory drugs and antioxidants for the management of pain, edema, trauma, and musculoskeletal disorders. Proteolytic enzyme preparations are widely

used in postoperative inflammation, sports injuries, arthritis, and soft tissue swelling because of their ability to reduce edema and inflammatory mediator activity [19].

In addition to their anti-inflammatory effects, proteolytic enzymes may improve microcirculation, facilitate removal of necrotic tissue, and enhance tissue repair. Their relatively favorable safety profile and potential opioid-sparing benefits have increased interest in their role as adjunctive agents in chronic pain conditions such as knee osteoarthritis [20].

7. MECHANISM OF ACTION OF PROTEOLYTIC ENZYMES

Proteolytic enzymes exert their therapeutic effects through multiple anti-inflammatory, anti-edematous, fibrinolytic, and immunomodulatory mechanisms. These enzymes modulate inflammatory pathways by hydrolysing protein mediators involved in inflammation and tissue injury. They can degrade inflammatory complexes, reduce vascular permeability, and facilitate removal of cellular debris from damaged tissues [19].

One of the major mechanisms involves suppression of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). By reducing the release and activity of these cytokines, proteolytic enzymes may decrease synovial inflammation and cartilage degradation associated with osteoarthritis [20].

Proteolytic enzymes also exhibit anti-edematous activity by promoting fibrinolysis and improving lymphatic drainage, thereby reducing tissue swelling and local pressure on pain-sensitive structures. Improvement in microcirculation enhances oxygen and nutrient delivery to inflamed tissues, facilitating tissue repair and recovery [21].

Additionally, bromelain and serratiopeptidase have been reported to inhibit neutrophil migration and reduce accumulation of inflammatory cells at sites of tissue injury. These actions contribute to decreased inflammatory pain and improved joint mobility [19].

Proteolytic enzymes may also possess indirect analgesic effects by decreasing bradykinin levels, reducing edema-induced nerve compression, and modulating pain mediator activity. Through these combined actions, enzyme therapy may improve joint stiffness, physical function, and overall

patient comfort in chronic inflammatory conditions such as knee osteoarthritis [22].

8. CLINICAL EVIDENCE OF PROTEOLYTIC ENZYMES IN OSTEOARTHRITIS

Several clinical studies have evaluated the efficacy of proteolytic enzymes in the management of osteoarthritis, particularly in reducing pain, inflammation, and functional disability. Bromelain-containing preparations have demonstrated significant improvements in pain scores, joint tenderness, and physical function, with some studies reporting efficacy comparable to nonsteroidal anti-inflammatory drugs (NSAIDs) [21].

Comparative clinical trials have suggested that oral enzyme combinations containing bromelain, trypsin, and rutin may provide symptomatic relief with a lower incidence of gastrointestinal adverse effects than conventional NSAID therapy [22]. Improvements in walking ability, joint

stiffness, and overall mobility have also been observed in patients receiving enzyme-based therapy.

Some studies have reported that proteolytic enzymes may reduce the requirement for additional analgesic medications, indicating a potential analgesic-sparing effect. Their anti-inflammatory and anti-edematous properties may contribute to better tolerability and enhanced patient compliance during long-term management of osteoarthritis [23].

Despite these promising findings, available evidence remains heterogeneous because of variations in study design, sample size, enzyme formulations, treatment duration, and outcome measures. Many studies are limited by small populations and lack of standardized protocols. Therefore, larger randomized controlled trials are required to establish definitive efficacy, optimal dosing strategies, and long-term safety of proteolytic enzyme therapy in osteoarthritis management [24].

Table 1. Summary of Major Clinical Studies on Proteolytic Enzymes in Osteoarthritis

Author (Year)	Study Design	Intervention	Key Findings
Brien et al. (2004)	Review	Bromelain	Improved pain and function; comparable efficacy to NSAIDs
Klein & Kullich (2000)	Clinical Study	Oral Enzyme Therapy	Reduced pain and improved mobility
Akhtar et al. (2004)	Comparative Trial	Enzyme Combination vs Diclofenac	Comparable efficacy with fewer GI adverse effects
Walker et al. (2002)	Clinical Trial	Bromelain	Dose-dependent pain reduction and improved well-being
Conrozier et al. (2021)	Review	Multimodal OA Therapy	Supported multimodal and opioid-sparing approaches

This table summarizes important clinical studies evaluating the efficacy and safety of proteolytic enzymes in osteoarthritis management. Most studies reported significant improvements in pain, joint function, and tolerability, supporting their role as adjunctive therapies.

9. PROTEOLYTIC ENZYMES AS ADJUNCTS TO TRAMADOL THERAPY

The combination of proteolytic enzymes with tramadol-based therapy may provide synergistic therapeutic benefits through simultaneous modulation of inflammatory and nociceptive pain pathways [23]. While

tramadol primarily acts centrally through μ -opioid receptor agonism and monoamine reuptake inhibition, proteolytic enzymes target peripheral inflammatory processes, thereby offering a multimodal approach to pain management.

By reducing inflammatory burden, tissue edema, and cytokine-mediated joint damage, enzyme therapy may enhance the overall analgesic response and potentially decrease the requirement for higher doses of tramadol. This analgesic-sparing effect could help minimize opioid-related adverse effects such as nausea, constipation, dizziness, sedation, and risk of dependence [24].

Adjunctive proteolytic enzyme therapy may

also improve joint mobility, physical function, and patient-reported quality of life in individuals with chronic knee osteoarthritis. Improved tolerability and reduced gastrointestinal toxicity compared with prolonged NSAID use may further enhance patient compliance during long-term therapy [25].

The integration of proteolytic enzymes into tramadol-based regimens aligns with current principles of opioid stewardship and multimodal analgesia, which emphasize optimizing pain control while minimizing opioid exposure. However, robust clinical evidence evaluating this combination strategy remains limited, and further randomized controlled studies are required to establish efficacy, safety, and standardized treatment protocols [26].

Table 2. Comparison of Tramadol Monotherapy versus Tramadol + Proteolytic Enzyme Therapy

Parameter	Tramadol Alone	Tramadol + Proteolytic Enzymes
Pain Relief	Moderate	Greater
Inflammation Control	Limited	Improved
Opioid Requirement	Higher	Reduced
Functional Outcome	Moderate	Better
Quality of Life	Moderate	Improved
Adverse Effects	More Common	Potentially Reduced

DISCUSSION

The present review highlights the growing interest in proteolytic enzymes as adjunctive agents in the management of knee osteoarthritis (KOA), particularly in the context of analgesic sparing and opioid stewardship. Current pharmacological therapies, including tramadol, provide symptomatic relief but are frequently associated with adverse effects and long-term safety concerns. Therefore, adjunctive therapies capable of enhancing analgesic efficacy while reducing opioid exposure are of considerable clinical importance.

Brien et al. reported that bromelain-containing preparations demonstrated clinically significant improvements in pain and functional outcomes among patients with osteoarthritis. Their review suggested that bromelain may exert anti-inflammatory and analgesic effects comparable to certain NSAIDs while maintaining a favorable safety

profile. These findings support the potential role of bromelain as a complementary therapy in chronic osteoarthritis management.

Klein and Kullich et al. evaluated oral enzyme therapy in painful osteoarthritis and observed significant reductions in pain intensity and improvements in joint mobility following short-term treatment. The authors concluded that enzyme preparations may provide effective symptomatic relief with good tolerability.

Akhtar et al. conducted a comparative study between an oral enzyme combination and diclofenac in patients with knee osteoarthritis. The study demonstrated comparable efficacy between the two treatment approaches in reducing pain and improving functional outcomes. Importantly, patients receiving enzyme therapy

experienced fewer gastrointestinal adverse effects, suggesting a potential safety advantage over long-term NSAID use.

Walker et al. investigated bromelain in individuals with mild acute knee pain and reported dose-dependent improvements in pain reduction and overall well-being. These findings further support the analgesic potential of bromelain and its possible application in chronic degenerative joint diseases.

Conrozier et al. emphasized the importance of multimodal approaches in osteoarthritis management. Their findings indicate that combining agents with different mechanisms of action may optimize pain control, improve patient adherence, and reduce dependence on opioid analgesics. In

this context, the combination of proteolytic enzymes with tramadol represents a promising multimodal strategy targeting both inflammatory and nociceptive pain pathways.

Collectively, available evidence suggests that proteolytic enzymes may contribute to improved pain management, enhanced physical function, and reduced analgesic requirements in knee osteoarthritis. However, heterogeneity among clinical studies, variations in enzyme formulations, and limited high-quality randomized controlled trials continue to restrict definitive conclusions. Further large-scale prospective studies are required to establish standardized dosing regimens, long-term safety, and the magnitude of opioid-sparing benefits associated with proteolytic enzyme therapy.

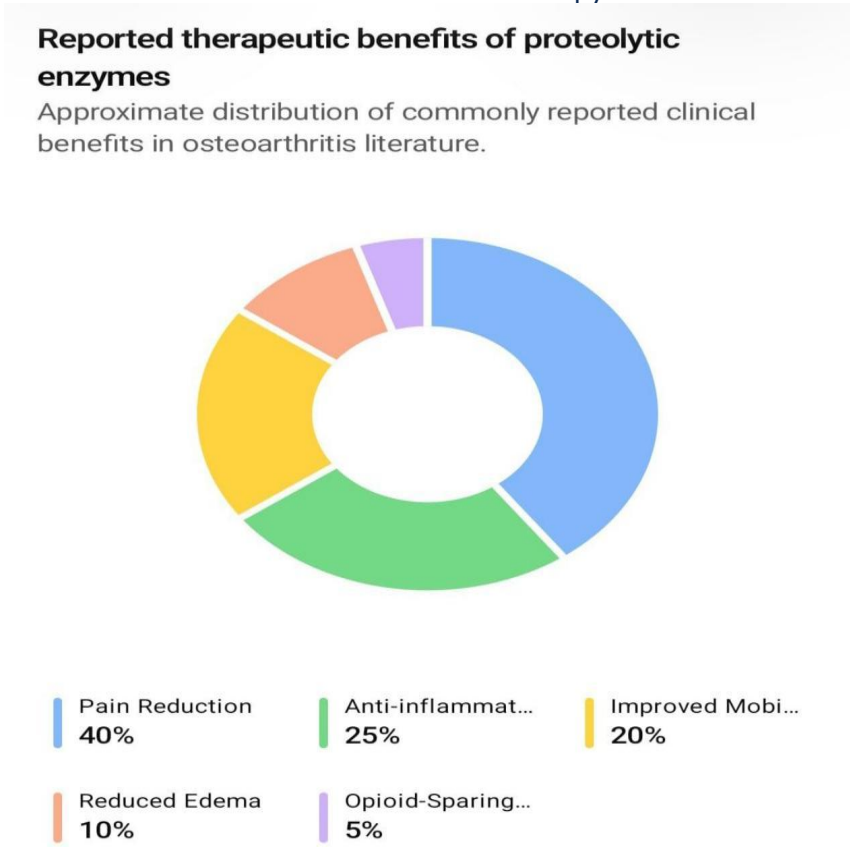


Figure 3: Distribution of Reported Benefits of Proteolytic Enzyme Therapy

The pie chart illustrates the commonly reported therapeutic benefits of proteolytic enzyme therapy in osteoarthritis. Pain reduction represents the most frequently

reported outcome, followed by anti-inflammatory effects and improvements in mobility.

Illustrative comparison of overall clinical improvement scores across selected studies.

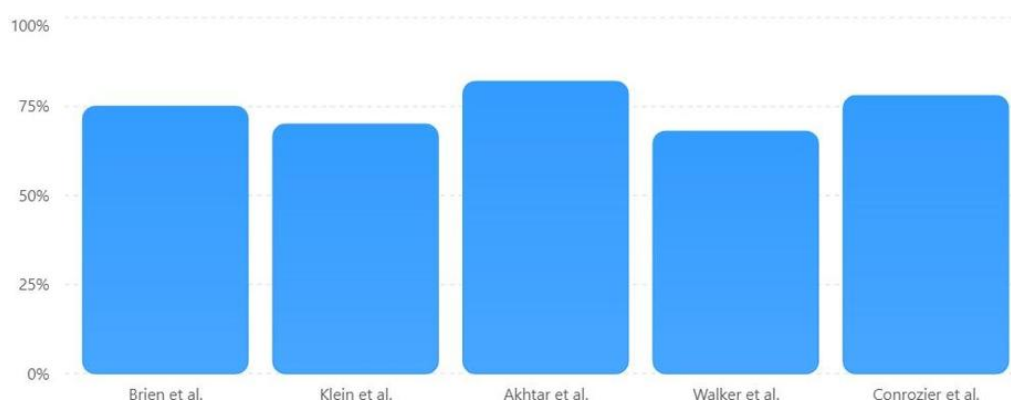


Figure 4: Comparative Clinical Outcomes Reported in Major Studies

The bar graph presents a visual comparison of the overall clinical benefits reported in major studies of proteolytic enzymes. The findings consistently demonstrate positive effects on pain reduction, functional improvement, and patient well-being.

10. RESEARCH GAP

Despite the promising therapeutic effects of proteolytic enzymes in knee osteoarthritis, several research gaps remain. Most available studies have evaluated proteolytic enzymes as independent or general adjunctive therapies, whereas direct evidence evaluating their combination with tramadol-based analgesic therapy is limited. Therefore, the specific contribution of proteolytic enzymes to reducing tramadol requirements remains insufficiently established. [30,39]

The available evidence is also heterogeneous with respect to enzyme preparations, dosage, treatment duration, study design, sample size, and outcome measures. Previous evidence on proteolytic enzymes has been limited by small sample sizes, inadequate methodological quality, and insufficient information regarding long-term safety. [30]

Another important research gap is the lack of standardized protocols for evaluating the analgesic-sparing effect of proteolytic enzymes. Future studies should clearly define outcomes such as daily tramadol dose, total cumulative opioid consumption, number of rescue analgesic doses, time to first rescue dose, pain intensity, and functional outcomes. Standardized clinical trial methodology and appropriate patient-reported and physical-performance outcomes are recommended for knee osteoarthritis research. [40]

Furthermore, limited evidence is available regarding the long-term safety, tolerability, drug interactions, and clinical effectiveness of proteolytic enzymes when used together with opioid analgesics. Large, adequately powered randomized controlled trials with longer follow-up are therefore required to determine their clinical utility and opioid-sparing potential. [30,39]

FUTURE RECOMMENDATIONS

Future research should focus on well-designed, adequately powered randomized controlled trials evaluating proteolytic enzymes specifically as adjuncts to tramadol-based therapy in patients with knee osteoarthritis. Studies should use appropriate randomization, blinding, standardized intervention protocols, clearly defined outcomes, and adequate follow-up periods. [40]

Future trials should standardize the type of proteolytic enzyme, dosage, treatment duration, and administration schedule to facilitate comparison between studies. Direct comparisons between tramadol-based therapy alone and tramadol combined with specific proteolytic enzyme preparations should also be performed.

Opioid-sparing outcomes should be incorporated as important study endpoints, including daily tramadol dose, total cumulative opioid consumption, number of rescue analgesic doses, time to first rescue dose, and percentage reduction in opioid exposure. This is particularly relevant because evidence regarding the efficacy and safety of tramadol in osteoarthritis remains mixed, with adverse effects and treatment discontinuation being important considerations. [39]

Future studies should also evaluate patient-centred outcomes such as VAS pain score,

WOMAC score, physical function, quality of life, mobility, and treatment adherence. Where appropriate, biochemical or inflammatory biomarkers may be incorporated to explore potential mechanisms and treatment response. [40,41]

Finally, future research should assess the long-term safety, tolerability, cost-effectiveness, and real-world effectiveness of proteolytic enzyme-based adjunctive therapy. Such evidence could help determine its potential role within multimodal osteoarthritis management, alongside established approaches such as exercise, weight management, self-management, and appropriate pharmacological therapy. [12]

CONCLUSION

Knee osteoarthritis remains a major cause of chronic pain, disability, and reduced quality of life worldwide. Although tramadol continues to play an important role in the management of moderate-to-severe osteoarthritic pain, concerns regarding opioid-related adverse effects, dependence, and long-term safety necessitate the development of analgesic-sparing strategies. Proteolytic enzymes, including bromelain, trypsin, chymotrypsin, and serratiopeptidase, possess anti-inflammatory, anti-edematous, and analgesic properties that may complement the pharmacological actions of tramadol.

Current evidence suggests that proteolytic enzymes can improve pain control, enhance physical function, reduce inflammation, and potentially decrease the requirement for additional analgesics. Their integration into tramadol-based therapy aligns with contemporary principles of multimodal analgesia and opioid stewardship. While existing clinical studies demonstrate promising outcomes, further high-quality randomized controlled trials are required to establish definitive efficacy, optimal dosing regimens, long-term safety, and opioid-sparing benefits.

Overall, proteolytic enzymes represent a promising adjunctive therapeutic approach in knee osteoarthritis and may contribute to safer and more effective long-term pain management strategies.

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