

Bromelain: Biological Activities and Therapeutic Potential

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Review Article

Volume: 10, Issue: 1

April, 2026

Pages: 73-80

Article History

Received: 02.02.2026

Accepted: 26.03.2026

Available online: 30.04.2026



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ABSTRACT

Bromelain is a plant-derived proteolytic enzyme complex obtained primarily from the stem of *Ananas comosus*. Beyond its protease activity, bromelain has been reported to modulate multiple biological pathways relevant to inflammation, haemostasis, immunity, tissue repair and host-pathogen interactions. Experimental data indicate that bromelain can downregulate pro-inflammatory mediators and cytokines through NF- κ B/MAPK-related signaling and reduced expression of inflammatory enzymes. It has also been associated with anti-oedematose effects linked to the kinin system. Bromelain has additionally been associated with antithrombotic and fibrinolytic actions, including effects on platelet aggregation, clotting times and fibrin(ogen) processing. In cancer-related models, bromelain has been described as influencing apoptosis, cell-cycle progression and metastatic behaviors through several signaling pathways. Bromelain-based enzymatic debridement has enabled clinical application in wound and burn management through selective eschar removal. Veterinary-oriented studies, although fewer than those in human medicine, suggest potential applications in inflammatory conditions, digestive disorders, musculoskeletal injuries and perioperative management; however, results are not uniformly positive and study designs, doses and preparations vary widely. This review summarizes the reported biological activities of bromelain, highlights evidence relevant to veterinary practice and underscores the need for well-designed, species-specific clinical trials to clarify efficacy, safety, optimal dosing and product standardization.

Keywords: bromelain, anti-inflammatory, immunomodulation, proteolytic enzyme, veterinary medicine

DOI: <https://doi.org/10.30704/http-www-jivs-net.1880601>

To cite this article: Yol, Ş.N. & Esen Gürsel, F. (2026). Bromelain: Biological Activities and Therapeutic Potential, Journal of Istanbul Veterinary Sciences, **10(1)**, 73-80. Abbreviated Title: **J. Istanbul vet. sci.**

Introduction

Bromelain is a plant-derived proteolytic enzyme complex that has attracted growing interest in biomedical research in recent years. This enzyme complex is primarily obtained from the fruit and, more notably, the stem tissues of the pineapple plant (*Ananas comosus*). In commercial preparations, the most widely used form is the derivative isolated from the stem, commonly referred to as “stem bromelain.”

Due to its proteolytic properties, which involve the degradation of proteins, bromelain has been extensively investigated as a regulatory and therapeutic agent in a wide range of biological processes, particularly those associated with disorders of the digestive system.

The pineapple plant, which thrives in tropical climates, has been utilized for centuries in traditional

medicine through various ethnobotanical practices. Indigenous populations of Central and South America have historically employed pineapple extracts for the management of digestive disturbances, wound healing, inflammatory conditions, and internal parasitic infections. Contemporary scientific investigations have provided evidence supporting some of these traditional applications and have demonstrated that the pharmacological properties of pineapple are largely attributable to the bromelain complex it contains.

Beyond its enzymatic activity, bromelain exerts pleiotropic effects on cellular signal transduction pathways, modulation of inflammatory responses, coagulation mechanisms, and immune system functions. Importantly, bromelain has been reported to be absorbed after oral administration and to retain biological activity *in vivo*, which may contribute to systemic effects (Maurer, 2001). Given its broad range of applications—from the food industry to wound management, oncology, and supportive therapy in autoimmune diseases—bromelain has emerged as a prominent natural compound with therapeutic potential supported by both traditional use and contemporary scientific evidence.

This review aims to comprehensively and critically examine the biological activities of bromelain across diverse physiological systems, highlighting its mechanisms of action and providing an integrated assessment of its potential therapeutic implications in veterinary medicine.

Anti-inflammatory Effects of Bromelain

Bromelain exhibits pronounced anti-inflammatory activity by targeting the production of key biochemical mediators involved in inflammatory processes, besides modulating associated intracellular signaling pathways. Its regulatory effects on fundamental inflammatory mechanisms, including cytokine secretion, prostaglandin synthesis, transcription factor activation and vascular permeability, have been demonstrated in numerous experimental studies, thereby supporting its therapeutic relevance. In particular, the inhibitory action of bromelain on prostaglandin synthesis via the arachidonic acid pathway is of considerable interest.

In lipopolysaccharide (LPS)-stimulated cellular models, bromelain treatment has been shown to significantly reduce the production of prostaglandin E₂ (PGE₂) and cyclooxygenase-2 (COX-2), with dose-

dependent effects observed, particularly in the human monocyte-derived THP-1 cell line (Huang et al., 2008).

Cytokine modulation represents another critical component of bromelain's anti-inflammatory action. In LPS-stimulated human THP-1 monocytes, bromelain has been reported to suppress the production of major pro-inflammatory cytokines, including IL-1 β , IL-6, and TNF- α (Huang et al., 2008). *In vivo*, anti-inflammatory activity has also been demonstrated in an ovalbumin-induced murine model of allergic airway disease (Secor et al., 2005). Inhibition of MAPK pathways along with suppression of NF- κ B signaling has been shown to downregulate COX-2 gene expression, thereby controlling inflammation at both transcriptional and mediator-release levels (Bhui et al., 2009). Such mechanisms are relevant not only to acute inflammatory responses but also to inflammation-associated carcinogenic processes.

In a kaolin-induced air-pouch inflammation model, bromelain reduced inflammatory exudation in a dose-dependent manner (Kumakura et al., 1988). Overall, the available evidence indicates that bromelain modulates multiple components of the inflammatory cascade, supporting its potential utility as a multi-target anti-inflammatory agent in veterinary clinical settings.

Antithrombotic and Fibrinolytic Effects of Bromelain

Bromelain is recognized as a natural compound with biologically active properties that extend beyond inflammation to include regulation of haemostatic balance. Due to its fibrinolytic and antithrombotic characteristics, bromelain has emerged as a potential therapeutic agent for the prevention of intravascular clot formation and the resolution of existing thrombi. These effects are mediated through multiple mechanisms, including enhanced plasminogen activation, inhibition of platelet aggregation, modulation of the coagulation cascade, and prolongation of clotting times.

Experimental evidence suggests that bromelain can influence fibrinolysis, including effects on fibrin(ogen) processing and coagulation parameters (Azarkan et al., 2020; Varilla et al., 2021). Earlier hypotheses also proposed antithrombotic potential (Felton, 1980). In addition to its capacity to degrade fibrin, bromelain has been reported to inhibit platelet aggregation and adhesion to the vascular endothelium, thereby reducing thrombus formation.

These antithrombotic effects have been further supported by findings from experimentally induced thrombosis models (Azarkan et al., 2020).

In addition to its anti-inflammatory properties, evidence indicates that bromelain modulates the haemostatic system through multiple complementary mechanisms, highlighting its potential relevance for antithrombotic therapeutic strategies in veterinary medicine.

Anticancer and Antimetastatic Effects of Bromelain

Bromelain is regarded as a multifunctional biomolecule capable of influencing tumor cell proliferation, invasion, and metastatic potential. Its anticancer effects are mediated through several biological processes, including regulation of the cell cycle, induction of apoptosis, modulation of tumor-associated signaling pathways, and suppression of metastatic mechanisms.

Studies on epidermoid carcinoma (A431) and malignant melanoma (A375) cell lines have demonstrated that bromelain significantly suppresses cellular proliferation by inducing cell cycle arrest at the G₂/M phase, an effect associated with inhibition of the NF- κ B signaling pathway (Bhui et al., 2012). Similarly, bromelain has been shown to block the cell cycle at the S and G₂/M phases in hepatocellular carcinoma HepG2 cells, resulting in a marked reduction in proliferative capacity (Murthy and Narsaiah, 2021).

In addition to its antiproliferative effects, bromelain primarily induces apoptosis via the mitochondrial pathway. Increased activation of caspase-3 and caspase-9, together with an elevated Bax/Bcl-2 ratio, are key molecular indicators of this process, as observed in A431 and A375 cells (Bhui et al., 2012). In HepG2 cells, apoptosis and DNA damage have been associated with the upregulation of p53 expression and the suppression of β -catenin, a critical component of the Wnt signaling pathway (Murthy and Narsaiah, 2021).

The anticancer activity of bromelain is further supported by its regulatory influence on intracellular signaling networks. The inhibition of NF- κ B nuclear translocation, the suppression of I κ B α phosphorylation and the downregulation of Akt activity all contribute to the reduction of COX-2 expression and the subsequent attenuation of tumor progression (Bhui et al., 2012).

Furthermore, bromelain interferes with multiple stages of the metastatic cascade by reducing

platelet–tumor cell interactions, suppressing matrix metalloproteinase-9 (MMP-9) expression and limiting angiogenesis by decreasing vascular endothelial growth factor (VEGF) levels. These findings suggest that bromelain may serve as a potential agent not only for inhibiting primary tumor growth but also for preventing metastatic dissemination (Bhui et al., 2012).

Effects of Bromelain on the Immune System

Bromelain is considered a natural biological agent that has immunomodulatory effects on the cellular and humoral components of the immune system. By suppressing pro-inflammatory cytokine production, regulating T and B lymphocyte activity and modulating innate immune responses, bromelain shows promise as a therapy for autoimmune disorders and chronic inflammatory conditions.

Studies using human monocyte-derived THP-1 cells have demonstrated that bromelain significantly reduces the secretion of key pro-inflammatory cytokines, such as IL-1 β , IL-6 and TNF- α , under lipopolysaccharide-stimulated conditions. These results suggest that bromelain could effectively attenuate systemic inflammatory responses (Huang et al., 2008).

Evidence from both *in vitro* and *in vivo* models indicates that bromelain reduces CD25 surface expression on CD4⁺ T lymphocytes, thereby limiting excessive cellular activation. This regulatory effect is thought to contribute to controlling dysregulated immune responses observed in inflammatory and autoimmune diseases (Secor et al., 2009).

In addition to its effects on cellular immunity, bromelain has been shown to modulate humoral immune responses. Animal studies have reported alterations in antibody production derived from B cells following bromelain administration, suggesting potential implications for vaccination efficacy and allergic reactions (Engwerda et al., 2001).

Current evidence indicates that bromelain contributes to immune homeostasis through regulatory effects on multiple immune pathways and may represent a versatile biological agent for the management of immune-mediated disorders.

Antimicrobial Effects of Bromelain

Bromelain, owing to its proteolytic enzyme composition, demonstrates biological activity in both host tissues and many bacteria. Bromelain has been reported to possess antibacterial, antiviral, and

antifungal properties, and has therefore gained attention as a potential adjunctive agent in antimicrobial therapies, particularly in combination with conventional antibiotics.

Bromelain has been reported to exhibit antibacterial activity against several Gram-positive and Gram-negative bacteria in experimental settings. Proposed mechanisms include proteolytic effects on protein targets involved in microbial adhesion and host-pathogen interactions (Rathnavelu et al., 2016). In addition to its antibacterial properties, bromelain has shown antiviral potential, particularly against enveloped viruses. *In vitro* studies have reported that bromelain may affect SARS-CoV-2-related entry factors, including spike protein and host cell components such as ACE2 and TMPRSS2 (Sagar et al., 2021).

Although data on antifungal activity are relatively limited, some studies suggest that bromelain may exert inhibitory effects against yeast species such as *Candida albicans*, potentially through proteolytic effects on fungal surface proteins and related virulence factors (Rathnavelu et al., 2016).

Bromelain has been demonstrated to augment the effectiveness of antimicrobial drugs in combination therapy. Synergistic effects have been reported with antibiotics such as amoxicillin, tetracycline, and chloramphenicol, resulting in improved antibacterial outcomes against resistant bacterial strains. This synergy has been proposed to involve increased tissue permeability and/or improved antibiotic penetration, as described in the literature (Rathnavelu et al., 2016; Chobotova et al., 2010).

Effects of Bromelain on the Digestive System

Bromelain, as a complex plant-derived proteolytic enzyme mixture, exerts multifaceted effects on the digestive system at both enzymatic and immunomodulatory levels. Its contribution to protein digestion, capacity to attenuate gastrointestinal inflammation, and protective effects against enterotoxins have led to its evaluation as a complementary agent in digestive system disorders.

Unlike pepsin and trypsin, bromelain is partially resistant to gastric acid, allowing it to reach the small intestine in an active form. In the small intestine, bromelain facilitates protein digestion by hydrolyzing proteins into peptides and amino acids, thereby supporting digestive processes, particularly in conditions involving endogenous enzyme

insufficiency (Maurer, 2001). Studies by Hale et al. have demonstrated that various commercial bromelain preparations retain substantial enzymatic activity under gastric conditions and exhibit structural stability within the digestive environment (Hale et al., 2005).

Beyond its proteolytic role, bromelain contributes to the regulation of gastrointestinal inflammatory responses. In chronic inflammatory conditions such as irritable bowel syndrome and inflammatory bowel disease, bromelain has been shown to modulate immune responses by suppressing IL-2 and interferon- γ production through regulation of T and B lymphocyte activity (Engwerda et al., 2001). This immunomodulatory action plays a role in controlling mucosal inflammation.

In a murine colitis model, the administration of bromelain significantly reduced inflammation within the colonic mucosa and limited the infiltration of inflammatory cells by inhibiting the expression of the adhesion molecule ICAM-1 (Hale et al., 2005). These results indicate that bromelain may contribute to preserving intestinal mucosal integrity and reducing inflammatory damage. Bromelain also exhibits anti-infective properties within the gastrointestinal tract. *In vitro* studies have demonstrated that bromelain reduces fluid secretion triggered by enterotoxins produced by *Vibrio cholerae* and *Escherichia coli*. This effect is attributed to enzymatic degradation of glycoproteins on the intestinal epithelial surface, thereby disrupting toxin binding sites (Mynott et al., 1997).

A notable characteristic of bromelain is its ability to enter the systemic circulation despite its proteinaceous nature. Its partial resistance to gastrointestinal proteolysis enables it to exert not only local digestive effects, but also systemic anti-inflammatory and immunomodulatory actions (Maurer, 2001). Collectively, these properties establish bromelain as a multifunctional biological agent in maintaining digestive system health.

Use of Bromelain in Wound and Burn Treatment

Bromelain possesses therapeutic potential in topical applications due to its selective proteolytic activity. In wound and burn management, bromelain-based formulations enable enzymatic debridement by selectively removing necrotic tissue while preserving viable tissue. This selective action promotes eschar removal and has been associated with favourable

clinical outcomes in burn care, potentially reducing the need for surgical debridement in selected cases (Hirche et al., 2020; Rosenberg et al., 2014). Furthermore, bromelain reduces levels of inflammatory mediators and alleviates oedema, thereby improving tissue oxygenation and nutrient diffusion. These effects contribute to enhanced epithelialization and limited scar formation, supporting its role as a non-surgical alternative in modern wound care (Rosenberg et al., 2014).

Effects of Bromelain on the Musculoskeletal System and Sports Injuries

Bromelain has been evaluated as a potential therapeutic agent in musculoskeletal disorders and sports-related soft tissue injuries due to its anti-inflammatory, tissue-regenerative effects, and proteolytic properties. Its effects on tendon and muscle tissues have been investigated in various experimental animal models.

In a Sprague–Dawley rat model of acute crush-type Achilles tendon injury, oral administration of bromelain at a dose of 7 mg/kg resulted in a significant increase in tendon cell numbers on day 14. However, no significant changes were observed in tendon mechanical strength or malondialdehyde levels, an indicator of oxidative stress. Compared with fresh pineapple juice, bromelain produced a more pronounced increase in tendon cell proliferation, suggesting a specific cellular-level benefit (Aiyegbusi et al., 2011).

Bromelain has been shown to modulate inflammatory processes in muscle tissue. In rat models, bromelain administration has been shown to significantly reduce levels of prostaglandin E₂ and substance P in inflammation-induced muscle injury. This indicates attenuation of inflammatory mediator release and potential facilitation of tissue recovery (Gaspani et al., 2002).

Functional effects on muscle performance have been demonstrated in hamster models, where bromelain administered at 5 mg/kg significantly increased tetanic contraction strength at both the early and later stages following injury. These findings suggest that bromelain may protect against muscle fibre damage and support functional recovery (Walker et al., 1992).

Potential Effects of Bromelain on the Cardiovascular System

Bromelain has been investigated among natural compounds with potential cardiovascular benefits because of its antithrombotic, antiaggregant, and vasculoprotective effects. Its modulation of platelet function, inhibition of thrombus formation and cardioprotective effects under ischaemic conditions suggest a potential role for bromelain in the prevention and supportive therapy of cardiovascular disease.

Inhibition of platelet activity is considered a key mechanism underlying bromelain's antithrombotic effects. Studies have demonstrated that bromelain effectively suppresses the formation of both arterial and venous thromboses (Pavan et al., 2012). *In vitro* studies have reported that bromelain can reduce platelet activity/aggregation (Gläser and Hilberg, 2006).

Cardioprotective effects have also been demonstrated in experimental ischaemia models. In isolated rat hearts, bromelain administration significantly reduced myocardial injury, an effect associated with increased AKT and FOXO3A phosphorylation, improved coronary flow and reduced infarct size (Juhász et al., 2008).

In thromboelastographic studies, bromelain significantly prolonged PT and aPTT values, as well as reducing ADP-induced platelet aggregation in human blood samples. However, the administration of low doses of bromelain in animal models has occasionally been associated with mild procoagulant tendencies, highlighting the importance of dose and physiological context in determining its net haemostatic effect (Kaur et al., 2016).

Protective Effects of Bromelain in Neurodegenerative Models

The antioxidant, anti-inflammatory and cholinergic-supportive properties of bromelain have prompted investigations into its potential to protect against neurodegenerative diseases in experimental models. Studies have demonstrated that bromelain can modulate oxidative stress, preserve acetylcholinesterase activity and reduce neuroinflammatory responses.

In a dichlorvos-induced neurotoxicity model in mice, for example, administration of bromelain significantly reduced markers of oxidative stress, such as thiobarbituric acid reactive substances and protein

carbonyl content, while increasing the activity of endogenous acetylcholinesterase in brain tissue (Chaudhary et al., 2018). These results suggest the preservation of cholinergic function and the relevance of bromelain for neurodegenerative disorders characterised by cognitive decline.

Similarly, in a rat model of neuroinflammation induced by sciatic nerve ligation, bromelain significantly reduced levels of pro-inflammatory mediators including IL-1 β , IL-6, TNF- α , prostaglandin E₂ and inducible nitric oxide synthase, while suppressing NF- κ B activity. Behavioural assessments further demonstrated improvements in pain sensitivity and anxiety-like behaviours following bromelain treatment (Bakare and Owoyele, 2021).

Results Concerning the Use of Bromelain in Veterinary Medicine

Digestive System and Microbiota (Dogs)

Randomised controlled studies involving healthy kennel dogs have shown that dietary formulations containing bromelain support gastrointestinal integrity without affecting body weight or condition scores. Significant reductions in faecal calprotectin and cortisol levels, along with increased concentrations of short-chain fatty acids, suggest beneficial effects on intestinal inflammation and stress-related parameters (Atuahene et al., 2023).

Microbiota analyses using 16S rRNA sequencing revealed the preservation of microbial diversity and an increased abundance of beneficial bacterial genera, including *Bifidobacterium*, *Lactobacillus* and *Pediococcus*. Notably, these effects persisted beyond the supplementation period, suggesting sustained modulation of gut microbial balance (Atuahene et al., 2024).

Mammary Lesions and Conservative Approaches (Cats)

In cats diagnosed with fibroadenomatous mammary changes, conservative treatment protocols incorporating bromelain-containing nutraceuticals have been associated with marked regression of mammary lesions. However, due to the use of combination therapies, bromelain is considered a supportive component rather than a sole therapeutic agent in these protocols (Marino et al., 2021).

Effects on Canine Chondrocytes (*In Vitro*)

In vitro studies on canine chondrocytes have demonstrated that bromelain reduces apoptosis, enhances mitotic activity, and suppresses expression of genes associated with cartilage matrix degradation, including TIMP-1 and MMP-3. These findings suggest a potential protective role for bromelain in osteoarthritic processes at the cellular level (Siengdee et al., 2010).

Bromelain-Derived Inhibitors in Allergen-Specific IgE Testing

In veterinary dermatology, bromelain-derived carbohydrate inhibitors have been shown to reduce cross-reactivity in allergen-specific IgE assays. The use of bromelain-derived carbohydrate cross-reactive determinant (BROM-CCD) has been shown to significantly improve the specificity of allergen-specific IgE testing without compromising the detection of clinically relevant allergens, thereby enhancing the reliability of allergy diagnostics in dogs and cats (Lee et al., 2020).

Postoperative Use and Analgesic Effects (Cats)

In cats undergoing ovariohysterectomy, short-term oral bromelain administration did not provide significant analgesic or anti-inflammatory benefits compared with placebo. Nevertheless, bromelain-treated cats exhibited faster recovery and no adverse effects on hepatic or renal function, indicating an acceptable safety profile for short-term postoperative use (Ribeiro et al., 2023).

Conclusion

Bromelain is a complex proteolytic enzyme mixture derived from *Ananas comosus* that exhibits a broad spectrum of biological activities and therapeutic potential. Current scientific evidence suggests anti-inflammatory, antithrombotic, anticancer, immunomodulatory, antimicrobial, and neuroprotective effects.

Despite the limited veterinary data, existing research in dogs and cats offers encouraging insights into the supportive role of bromelain in gastrointestinal health, microbiota modulation, cartilage preservation, and the diagnostic accuracy of allergy testing. While bromelain does not appear to function as a standalone analgesic in postoperative settings, its favourable safety profile warrants further investigation.

Overall, well-designed, species-specific randomised controlled clinical trials are needed to clarify the therapeutic role of bromelain in veterinary medicine.

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