INFORMATICS JOURNALS

Short Review

Journal of Natural Remedies
DOI: 10.18311/jnr/2026/54323

eISSN: 2320-3358 | Vol 26(8), 2026 | pp. 2015-2025

Therapeutic Potential of Pineapple Bromelain in Ocular Disorders

Rahul Debnath[1], Shamit Pal[2], Om Shankar Kamat[3], Ankit Sharma[4], Rajib Mandal[1*] and Nilendu Pal[5]

[1]Faculty of Allied and Healthcare Sciences, Assam down town University, Panikhaiti, Guwahati - 781026, Assam, India; optmrajib.mandal@gmail.com

[2]Department of Optometry (CSHS), Chitkara University, Rajpura, Patiala - 140401, Punjab, India

[3]Department of Optometry, Maharishi Markandeshwar University, Mullana, Ambala - 133203, Haryana, India,

[4]Department of Optometry, Om Sterling Global University, Hisar - 125005, Haryana, India

[5]Department of Optometry, Maharishi Markandeshwar University, Solan - 173229, Himachal Pradesh, India

Abstract

Background: Bromelain, a proteolytic enzyme complex derived from *Ananas comosus (L.) Merr.* has been widely studied for its anti-inflammatory, antioxidant, proteolytic, immunomodulatory, anti-fibrotic, and anti-microbial properties. Preclinical evidence suggests that bromelain exerts protective effects in ocular disorders by attenuating oxidative stress, suppressing inflammatory signalling, remodelling the extracellular matrix, and modulating immune responses. **Aim:** This review summarises the *in vitro*, *in vivo*, and clinical evidence on the ocular therapeutic potential of bromelain, outlining its mechanisms of action and pharmacokinetic considerations. **Methods:** A literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar using the keywords "bromelain," "ocular," "eye," and "vitreolysis" for studies published between January 1980 and December 2025. **Results:** Experimental studies demonstrate that bromelain inhibits NF-κB activation, increases antioxidant enzyme activity, promotes vitreous collagen degradation, and reduces pro-fibrotic signalling via TGF-β/Smad pathway modulation. Clinical studies, particularly those involving bromelain-containing enzyme formulations, report faster clearance of vitreous haemorrhage, reduction of symptomatic floaters, and improved visual function, with a favourable safety profile. **Conclusion:** Despite these promising findings, current evidence is limited by small sample sizes, heterogeneity in formulations, and a lack of trials evaluating bromelain monotherapy in ocular disease. Further research should focus on standardised preparations, advanced ocular delivery systems, and well-powered randomised controlled trials to establish clinical efficacy and safety.

Major Findings: Bromelain shows promising therapeutic potential in eye-related problems owing to its anti-inflammatory, antioxidant, and proteolytic properties. Current evidence suggests that it may be a very good alternative to clear vitreous haemorrhage and reduce symptomatic vitreous opacities. Nevertheless, additional standardised clinical trials are needed to confirm its efficacy in ocular therapy.

Keywords: Bromelain, Ocular Disease, Pineapple, Vitreolysis

Abbreviations: COX-2 - Cyclooxygenase-2; ECM - Extracellular Matrix; GPx - Glutathione Peroxidase; IL-1β - Interleukin-1 beta; NF-κB - Nuclear Factor kappa; BROS - Reactive Oxygen Species; SOD - Superoxide Dismutase; TGF-β - Transforming Growth Factor beta.

(Article Chronicle: Article Received on: 09.01.2026; Revised on: 18.06.2026; Accepted on: 07.07.2026)

1. Introduction

Ocular diseases, such as symptomatic vitreous opacities, retinal inflammatory disorders, and postoperative complications, remain major causes of visual morbidity worldwide. Symptomatic floaters alone affect an estimated 76% of individuals over a lifetime, with approximately one-third reporting

*Author for correspondence

significant interference with visual function and quality of life[1]. Current therapeutic approaches, such as pars plana vitrectomy and Nd:YAG laser vitreolysis, are effective in selected cases but are associated with risks, including cataract formation, retinal detachment, and intraocular pressure spikes[2]. Consequently, there is a pressing need for non-invasive, pharmacologically targeted interventions capable of alleviating symptoms while preserving ocular tissue integrity.

Bromelain, a proteolytic enzyme complex derived from the stem and fruit of pineapple, has been traditionally employed for its anti-inflammatory, analgesic, and fibrinolytic properties in musculoskeletal, cardiovascular, and dermatological conditions[3]. Its therapeutic versatility is attributed to multiple mechanisms, including inhibition of nuclear factor-κB (NF-κB) signalling, modulation of cyclooxygenase-2 (COX-2) and prostaglandin synthesis, regulation of pro- and anti-inflammatory cytokines, and proteolytic degradation of extracellular matrix components[4,5]. Importantly, bromelain exhibits high oral tolerability and favourable systemic safety profiles, as evidenced in multiple randomised clinical trials and meta-analyses[5].

Emerging evidence suggests that bromelain's pharmacological actions may extend to ocular tissues. In a cisplatin-induced ocular toxicity model, oral bromelain supplementation attenuated oxidative stress markers Malondialdehyde (MDA), Reactive Oxygen Species (ROS), increased Superoxide Dismutase (SOD) activity, and suppressed NF-κB, Interleukin-1β (IL-1β), and Tumour Necrosis Factor-α (TNF-α) expression, thereby preserving corneal and retinal architecture[6]. Clinical pilot trials using mixed fruit enzyme supplements containing bromelain have reported reductions in symptomatic vitreous opacities and vitreous haemorrhage-related floaters, with improvements in contrast sensitivity and patient-reported visual function[7,8]. These findings highlight bromelain as a candidate for pharmacological vitreolysis and broader ocular anti-inflammatory therapy.

Given its multifaceted mechanisms, documented systemic safety, and emerging ocular efficacy, bromelain warrants critical evaluation for translation into ophthalmic practice. This review synthesises current preclinical and clinical evidence, elucidates the underlying molecular pathways, and identifies key challenges and opportunities for developing bromelain-based ocular therapeutics.

2. Search Strategy

A comprehensive literature search was conducted to identify preclinical and clinical studies evaluating bromelain in ocular disorders and related mechanistic contexts, including pharmacokinetics and biochemical pathways. Searches were performed in PubMed, Scopus, Web of Science, and Google Scholar for articles published from January 1980 to December 2025, prioritising recent studies while including earlier seminal works. Search strings combined Medical Subject Headings (MeSH) and free-text terms: ("bromelain" OR "ananas comosus" OR "pineapple enzyme" OR "fruit enzyme") AND ("ocular" OR "eye" OR "vitreous" OR "retina" OR "cornea" OR "macula" OR "optic nerve") AND ("oxidative stress" OR "inflammation" OR "proteolysis" OR "vitreolysis" OR "extracellular matrix") AND ("preclinical" OR "animal model" OR "*in vitro*" OR "clinical trial" OR "randomised" OR "observational study"). Eligible studies included original peer-reviewed research in English, encompassing *in vitro*, animal, and human investigations, as well as pharmacokinetic and mechanistic analyses relevant to ocular bioavailability or action. Exclusion criteria comprised non-peer-reviewed sources, conference abstracts without full datasets, non-ocular studies without mechanistic relevance, and investigations using pineapple extracts without quantification or confirmation of bromelain content. Additional search measures included manual screening of reference lists from retrieved articles, cross-checking citations in relevant reviews, and searching grey literature for ongoing clinical trials via ClinicalTrials.gov.

3. Preclinical Evidence

Experimental evidence supporting bromelain's ocular applications is limited but growing (Table 1). The most compelling data come from animal models of chemically induced ocular injury and *in vitro* vitreous gel studies. These models highlight bromelain's antioxidant, anti-inflammatory, and proteolytic actions, all of which are relevant to pathologies such as vitreous degeneration, intraocular haemorrhage, and oxidative retinal injury.

Bromelain was administered orally (50 or 100 mg/kg/day) in a rat model of cisplatin-induced ocular toxicity for 14 days[8]. Treatment resulted in a significant

reduction in oxidative stress markers, including MDA and Total Oxidant Status (TOS), alongside increased SOD activity. Pro-inflammatory cytokines interleukin-1β (IL-1β) and TNF-α, as well as nuclear factor-κB (NF-κB) expression, were markedly suppressed, leading to preservation of corneal and retinal histoarchitecture.

The proteolytic vitreolysis potential was demonstrated in an *in vitro* porcine vitreous model[9]. Bromelain treatment reduced forward light scattering, suggesting the degradation of collagen fibril aggregates, a mechanism potentially beneficial for patients with symptomatic vitreous opacities. This enzymatic vitreolysis aligns with clinical observations from mixed enzyme supplementation trials, in which bromelain is a key component.

While these findings underscore bromelain's capacity to mitigate oxidative and inflammatory injury and to alter vitreous matrix structure, the paucity of ocular-focused preclinical studies remains a limitation. Future research should explore additional models, such as diabetic retinopathy, uveitis, and ischemia-reperfusion injury, incorporating pharmacokinetic endpoints to determine ocular tissue bioavailability. The preclinical evidence supporting the antioxidant, anti-inflammatory, and proteolytic effects of bromelain in ocular disease models is summarised in Table 1.

4. Clinical Evidence

Human clinical data on bromelain's ocular applications remain sparse; however, early studies, particularly in the context of symptomatic vitreous opacities and vitreous haemorrhage, are promising (Table 2). Most involve oral supplementation with Mixed Fruit Enzyme (MFE) formulations containing bromelain in combination with papain and ficin, capitalising on the proteolytic degradation of vitreous collagen aggregates.

A randomised controlled trial involving 224 patients with Symptomatic Vitreous Opacities (SVOs) was conducted. Participants received oral MFE capsules (bromelain 190 mg, papain 95 mg, ficin 95 mg) daily for three months. The MFE group demonstrated significant reductions in SVO density on objective imaging, improved contrast sensitivity, and fewer subjective floater complaints compared to the controls. No serious adverse events were reported, supporting the safety of long-term oral enzyme supplementation in this context[10].

A subsequent clinical study examined the same MFE formulation in patients with vitreous haemorrhage-induced floaters[7]. Over three months, enzyme-treated patients experienced more rapid clearance of vitreous opacities and better visual function recovery than

Table 1. Preclinical studies of pineapple bromelain in ocular disease models

Model	Intervention	Dose / Duration	Key Findings	References
Rat, cisplatin-induced ocular toxicity	Oral bromelain	50 or 100 mg/kg/day for 14 days	Reduced oxidative stress markers; increased antioxidant enzymes; suppression of inflammatory cytokines; preservation of corneal and retinal structure	[8]
In vitro porcine vitreous model	Bromelain incubation	0.5-2 mg/mL for 2 h	Reduced forward light scattering indicating collagen fibril degradation	[9]

Notes: MDA, malondialdehyde; TOS, total oxidant status; SOD, superoxide dismutase; IL-1β, interleukin-1 beta; TNF-α, tumour necrosis factor alpha; NF-κB, nuclear factor kappa B. Currently, ocular-specific preclinical evidence for bromelain remains limited.

Table 2. Clinical studies evaluating bromelain-containing formulations in ocular disorders

Study design	Population	Intervention	Duration	Key outcomes	References
Prospective clinical study	Adults with vitreous haemorrhage-induced floaters	Oral Mixed Fruit Enzyme (MFE) formulation containing bromelain	3 months	Faster clearance of vitreous opacities; improved visual recovery; good tolerability	[7]
Randomised controlled trial	Adults with symptomatic vitreous opacities (n = 224)	Oral MFE (bromelain 190 mg, papain 95 mg, ficin 95 mg) daily	3 months	Reduced floater density; improved contrast sensitivity and subjective symptoms; no serious adverse events	[10]

Notes: MFE, mixed fruit enzyme formulation; RCT, randomised controlled trial. Most clinical studies evaluated bromelain as part of multi-enzyme formulations.

those receiving standard care alone. The therapeutic benefit was attributed to the enzymatic degradation of fibrin and collagen, potentially accelerating vitreous remodelling and the absorption of haemorrhagic debris.

These trials, while encouraging, have limitations including relatively small sample sizes for the haemorrhage subgroup, lack of masking in some analyses, and the absence of bromelain monotherapy arms. Nevertheless, they provide preliminary human evidence that bromelain-containing formulations can improve visual outcomes in selected ocular conditions. The available clinical studies evaluating bromelain-containing formulations in vitreous-related ocular disorders are outlined in Table 2.

5. Mechanistic Insights

The pharmacological activities of bromelain relevant to ocular health are underpinned by its multifaceted biochemical profile, which includes proteolytic enzymes, peroxidases, acid phosphatases, cellulases, and various protease inhibitors[11,12]. These components contribute to a broad spectrum of biological effects, including antioxidant, anti-inflammatory, fibrinolytic, and immunomodulatory actions[2,13].

5.1 Modulation of Oxidative Stress and Inflammatory Pathways

Oxidative stress and chronic inflammation are central pathogenic mechanisms in a wide range of ocular diseases, including age-related vitreous degeneration and retinal ischemia[14,15]. Bromelain mitigates these processes through a coordinated influence on inflammatory signalling and redox homeostasis. It downregulates the nuclear translocation of the NF-κB p65 subunit, thereby suppressing the transcription of pro-inflammatory mediators, including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and cyclooxygenase-2 (COX-2)[5,6]. In parallel, bromelain enhances endogenous antioxidant defences, increasing the activity of SOD and Glutathione Peroxidase (GPx) while reducing MDA and ROS levels in ocular and systemic models[6,16]. Through modulation of the arachidonic acid cascade, bromelain also inhibits Prostaglandin E_2 (PGE_2) synthesis, contributing further to its anti-inflammatory profile[17].

5.2 Proteolytic Vitreolysis and Extracellular Matrix Remodelling

The vitreous body is primarily composed of collagen type II fibrils, hyaluronan, and water, and undergoes structural alterations with ageing or pathology, leading to collagen aggregation, light scattering, and the development of symptomatic floaters[18]. Bromelain's proteolytic properties enable the enzymatic cleavage of collagen and fibrin aggregates, as shown in porcine vitreous models, where exposure reduced forward light scattering[9]. Clinically, bromelain-containing formulations have been linked to faster resolution of vitreous haemorrhage, an effect likely mediated by fibrinolysis and protease-driven clot degradation[11]. These findings support bromelain's potential as a minimally invasive alternative to surgical or laser-based vitreolysis.

5.3 Immunomodulation and Tissue Repair

Bromelain exerts immunomodulatory effects that may facilitate ocular tissue repair, beyond its anti-inflammatory capacity. It shifts the cytokine milieu toward an anti-inflammatory profile, increasing interleukin-10 (IL-10) while reducing interleukin-6 (IL-6) and interferon-γ (IFN-γ), thus promoting conditions favourable for wound healing[19,20]. Furthermore, bromelain enhances Natural Killer (NK) cell activity and stimulates lymphocyte migration, which could improve immune surveillance and accelerate resolution of ocular inflammation[21]. These combined actions suggest that bromelain not only attenuates pathogenic inflammatory processes but also actively supports the restoration of tissue integrity.

5.4 Pharmacokinetics and Bioavailability Considerations

Bromelain is orally bioavailable in small amounts, with proteolytically active fractions detectable in plasma within 1-3 h after ingestion and a reported plasma half-life of approximately 6-9 hours[11,22-28]. Although systemic anti-inflammatory effects are well documented, direct ocular tissue concentrations following oral dosing remain unknown. Animal studies indicate that formulation strategies, such as chitosan nanoparticles and lipid-polymer hybrid carriers, enhance bromelain stability, prolong systemic exposure, and improve tissue distribution compared

with free bromelain[20,29-33]. In parallel, *in vitro* and *ex vivo* investigations using mucoadhesive hydrogels and ocular delivery platforms have demonstrated sustained release and improved corneal permeation, supporting the feasibility of topical bromelain delivery for anterior segment ocular disorders[34-36]. Potential delivery optimisations therefore include nanoencapsulation, mucoadhesive ocular inserts, and periocular administration to enhance local ocular bioavailability[37]. Key pharmacokinetic parameters and formulation strategies relevant to ocular research are summarised in Table 3.

5.5 Anti-fibrotic Actions

Fibrosis is a common pathological endpoint in various ocular conditions, including Proliferative Vitreoretinopathy (PVR), post-surgical conjunctival scarring in glaucoma filtration surgery, and subretinal fibrosis in neovascular age-related macular degeneration[38,39]. Bromelain has demonstrated anti-fibrotic potential by modulating fibroblast proliferation, extracellular matrix deposition, and myofibroblast differentiation.

In vitro studies have shown that bromelain reduces the expression of α-smooth muscle actin (α-SMA) and fibronectin in transforming growth factor-β (TGF-β)-stimulated fibroblasts, indicating the suppression of myofibroblast formation[40]. In animal models, bromelain treatment decreased collagen types I and III deposition in scar tissue, possibly via downregulation of the TGF-β/Smad signalling pathways[41].

These effects may have relevance in ocular surgery, where postoperative fibrosis remains a major cause of failure in trabeculectomy and retinal detachment repair. Although no published ocular-specific anti-fibrotic studies exist for bromelain, its systemic anti-fibrotic activity supports further investigation as an adjunct to current anti-scarring agents, such as mitomycin C and 5-fluorouracil[42].

5.6 Anti-microbial and Anti-biofilm Activity

Bromelain possesses intrinsic anti-microbial effects, partly attributed to its proteolytic degradation of bacterial cell surface proteins and biofilm matrices[16,33]. *In vitro*, bromelain disrupts *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms, reducing biomass and enhancing susceptibility to conventional antibiotics[20,43].

These properties may be relevant in ocular infections where biofilms contribute to persistent disease, such as bacterial keratitis, post-surgical endophthalmitis, and contact lens-associated microbial keratitis[44]. Additionally, bromelain synergises with antibiotics, such as amoxicillin and ciprofloxacin, against resistant bacterial strains, suggesting its potential as an adjunctive therapy for ocular surface infections[43]. Although direct

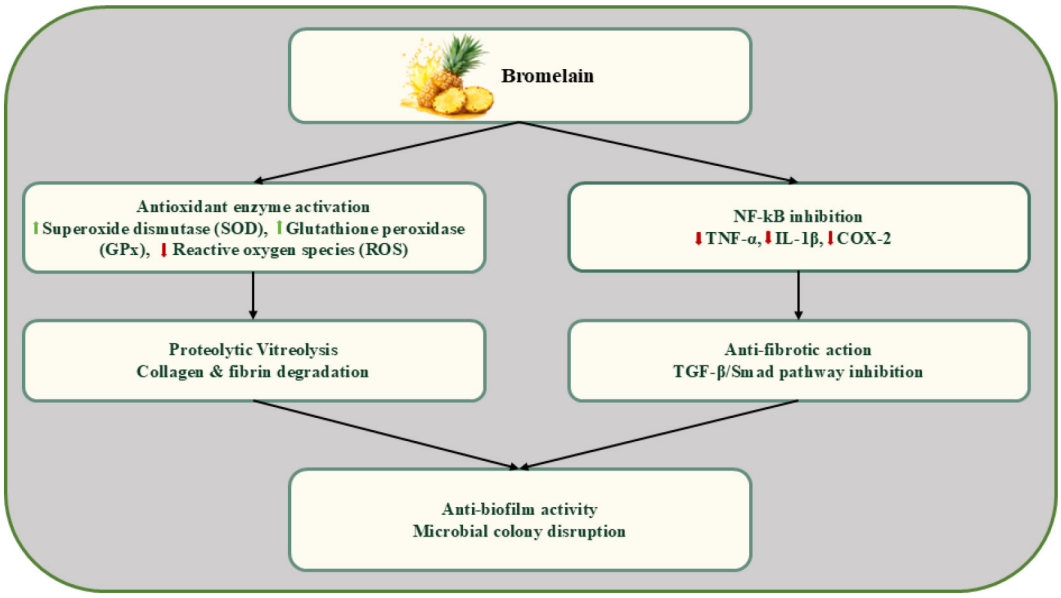


Figure 1. Pineapple bromelain in the management of ocular disorders. Pineapple bromelain enhances antioxidant enzymes like SOD and GPx and inhibits NF-κB-mediated inflammation markers like TNF-α, IL-1β, and COX-2.

Table 3. Pharmacokinetic characteristics and formulation strategies of bromelain relevant to ocular research

Model/ population	Formulation/ approach	Route of administration	Key pharmacokinetic or delivery findings	Relevance to ocular research	References
Human volunteers	Crude or enteric-coated bromelain	Oral	Proteolytically active bromelain detectable in plasma; peak levels within 1-3 h; plasma half-life approximately 6-9 h	Confirms systemic absorption and feasibility of oral bromelain for ocular indications	22-28
Animal models	Bromelain with excipients or nanocarrier systems (chitosan nanoparticles, lipid-polymer hybrid nanoparticles)	Oral	Enhanced plasma stability, prolonged systemic exposure, and improved tissue distribution compared with free bromelain	Supports formulation-based strategies to enhance ocular bioavailability, particularly for posterior segment targets	20, 29-32,43
In vitro and *ex vivo* ocular models	Bromelain-loaded mucoadhesive hydrogels and ocular delivery platforms	Topical ocular	Sustained drug release and improved corneal permeation with prolonged ocular surface residence time	Demonstrates feasibility of topical bromelain delivery for anterior segment ocular disorders	34-36

Notes: h - hours

clinical evidence in ophthalmology is lacking, its broad-spectrum anti-biofilm and anti-inflammatory profile supports exploration in ocular prophylaxis and treatment, particularly in cases in which microbial persistence impedes healing. Figure 1 summarises the key antioxidant, anti-inflammatory, proteolytic, and anti-fibrotic actions of bromelain in ocular disorders.

6. Chemical Constituents and Pharmacokinetics

Bromelain is a complex mixture of proteolytic and non-proteolytic components derived primarily from pineapple stems and fruits. The major active constituents are thiol endopeptidases (EC 3.4.22.32), collectively referred to as stem bromelain and fruit bromelain, which differ in molecular weight, isoelectric point, and substrate specificity[45]. Minor components include phosphatases, glucosidases, peroxidases, cellulases, and protease inhibitors[12,20].

Bromelain is water-soluble and stable in a broad pH range (4-8), but is susceptible to heat inactivation above 60°C[4,43]. Its activity is typically expressed in Gelatin Digesting Units (GDU) or Milk Clotting Units (MCU), which are important for standardising therapeutic preparations. Commercial products vary in proteolytic activity and may contain different ratios of stem and fruit bromelain, which can influence pharmacological effects[4].

Following oral administration, bromelain is absorbed in its proteolytically active form, with peak plasma concentrations occurring within 1 h and a plasma half-life of 6-9 h[11,24]. Bioavailability is estimated to be low (approx. 40% of ingested activity), yet measurable enzyme activity in plasma suggests translocation via a paracellular transport pathway or receptor-mediated endocytosis[46]. Bromelain exhibits wide tissue distribution, with detection in plasma, liver, kidney, and in some studies, ocular tissues[37]. It undergoes renal clearance, and no significant accumulation has been reported with repeated dosing[11].

Pharmacokinetic parameters can be improved using advanced delivery systems, including nanoencapsulation, mucoadhesive gels, and ocular-targeted inserts (Table 3). These approaches may enable higher local concentrations in ocular tissues, potentially enhancing the therapeutic efficacy for posterior segment diseases.

7. Discussion

The present synthesis highlights bromelain as a promising candidate for non-invasive ocular therapy, particularly in conditions characterised by vitreous opacities,

vitreous haemorrhage, and oxidative or inflammatory retinal injury. Its pleiotropic mechanisms-spanning antioxidant activity, suppression of pro-inflammatory mediators, proteolytic remodelling of extracellular matrix components, and immunomodulation address multiple pathophysiological pathways that converge in common ocular diseases[3,5,13].

Clinical trials provide early human evidence for bromelain-containing formulations in improving visual outcomes, with reductions in floater burden and enhanced clearance of vitreous hemorrhage[8,47]. These findings align with preclinical observations of reduced collagen aggregation and fibrin degradation in the vitreous[13] and mitigation of oxidative and inflammatory damage in ocular tissues[6]. Importantly, bromelain's oral administration route and favourable safety profile distinguish it from invasive surgical options such as pars plana vitrectomy or Nd:YAG laser vitreolysis, which carry risks including retinal detachment and cataract formation[1,2].

Direct comparison with established standard treatments places these early findings in a clinical context. Nd:YAG laser vitreolysis, the most widely used non-surgical alternative, was evaluated in a sham-controlled randomised trial in which 53% of treated eyes reported significant or complete symptomatic improvement at six months, compared with none of the sham-treated eyes, with no clinically relevant adverse events[48]; however, this trial enrolled only 52 patients, and its durability beyond six months remains uncertain. Pars plana vitrectomy, the definitive surgical option, achieves higher and more consistent rates of symptom resolution; pooled data from 18 studies (2,077 eyes) indicate that at least 90% of patients report satisfaction or symptomatic relief[49], and a large single-center series similarly reported 84-85 % complete or substantial symptom resolution[50]; however, this benefit is offset by a cumulative retinal detachment risk approaching 11% and additional risks of cystoid macular edema, epiretinal membrane formation, and glaucoma. A further useful benchmark is ocriplasmin, the only enzymatic vitreolysis agent to have received regulatory approval for an ocular indication (symptomatic vitreomacular adhesion); in the pivotal MIVI-TRUST trials, intravitreal ocriplasmin resolved vitreomacular adhesion in 26.5% of eyes versus 10.1% with placebo, a modest absolute benefit accompanied by self-reported ocular adverse events (floaters, photopsia, dyschromatopsia) in over two-thirds of treated eyes[51]. Set against these benchmarks, the oral bromelain-containing MFE formulations evaluated to date report comparatively favorable safety and tolerability and avoid the procedural risks of surgery or laser, but the magnitude of their effect on validated, vision-related quality-of-life measures has not been benchmarked against YAG laser vitreolysis, vitrectomy, or ocriplasmin in a head-to-head or even cross-trial calibrated fashion, since the bromelain trials to date[7,10] used floater density and contrast sensitivity rather than the NEI VFQ-25 or comparable instruments used in the surgical and laser literature. Consequently, bromelain cannot yet be positioned as superior, equivalent, or simply adjunctive to these standard interventions; rather, the current evidence supports a hypothesis-generating role for bromelain as a non-invasive option warranting head-to-head evaluation, particularly in patients who are poor candidates for surgery or laser, or who decline invasive intervention for mild-to-moderate symptoms.

Nevertheless, several limitations temper immediate clinical adoption and should guide the interpretation of the existing evidence. First, most human studies have investigated bromelain within multi-enzyme formulations together with papain and ficin, making it impossible to isolate bromelain's individual contribution to the observed clinical effects; compounding this, the two principal clinical trials originate from overlapping investigator groups using a single proprietary formulation, raising the possibility of selection and publication bias and limiting independent replication. Second, outcome assessment has not been standardised across studies: bromelain trials have relied on floater density on imaging, contrast sensitivity, and study-specific symptom scales, whereas the comparator literature on YAG laser vitreolysis and vitrectomy more often reports validated instruments such as the NEI VFQ-25[48,49], precluding direct, calibrated comparison of effect sizes across treatment modalities. Third, neither of the two key bromelain trials incorporated a placebo- or sham-controlled, fully masked design, introducing the possibility of expectation and observer bias for outcomes that are inherently subjective and known to fluctuate over time. Fourth, follow-up has been limited to three months, which is insufficient to establish whether benefits persist after

supplementation is discontinued or whether efficacy is maintained in conditions with a more chronic or progressive natural history. Fifth, bioavailability data in ocular tissues remain sparse; although proteolytically active bromelain has been detected in plasma after oral dosing[52], its direct concentration within the vitreous, aqueous humour, or retina after oral or topical administration has not been measured in humans, so adequate target-tissue exposure remains an assumption rather than a demonstrated fact. Sixth, because bromelain-containing products are typically marketed as nutraceuticals or dietary supplements rather than as regulated pharmaceuticals, proteolytic activity, purity, and the ratio of stem to fruit bromelain vary considerably between manufacturers and batches, undermining reproducibility and complicating any future regulatory pathway unless activity is harmonised using standardised units such as GDU or MCU. Seventh, long-term safety in ocular populations, particularly those with compromised retinal integrity, high myopia, or pre-existing vitreoretinal traction, has not been studied, and a theoretical risk of excessive proteolysis at the vitreoretinal interface or retinal basement membrane has not been excluded. Finally, no cost-effectiveness analyses comparing bromelain-based formulations with YAG laser vitreolysis, vitrectomy, or observation currently exist, information that will be necessary before any role in the treatment pathway can be defined.

Future research should prioritise randomised, sham- or active-controlled trials of bromelain monotherapy, with standardised dosing and proteolytic activity units (GDU or MCU) to enable reproducibility, an active or standard-of-care comparator arm (*e.g.*, YAG laser vitreolysis, vitrectomy, or observation), and validated patient-reported outcome measures such as the NEI VFQ-25 to permit direct, calibrated benchmarking against existing treatments. Mechanistic studies using advanced ocular imaging, molecular profiling, and pharmacokinetic modelling could elucidate tissue-specific distribution and clarify therapeutic windows. Innovative delivery platforms, such as nanoencapsulation or sustained-release intraocular inserts, may overcome bioavailability limitations and enhance local efficacy[53].

From a translational perspective, bromelain's broad anti-inflammatory and matrix-remodelling properties may also have utility in other ocular diseases, including proliferative diabetic retinopathy, retinal vein occlusion, and post-surgical fibrosis. However, the therapeutic index for enzymatic vitreolysis must be carefully defined to balance efficacy with preservation of vitreoretinal structure and function.

In summary, pineapple bromelain is a biologically plausible, safe, and potentially effective adjunct or alternative to invasive vitreolysis procedures. The convergence of mechanistic rationale, encouraging preclinical data, and early human efficacy signals justifies continued clinical investigation. If future studies confirm its benefits, bromelain could expand the pharmacological armamentarium for managing vitreous and retinal disorders, providing patients with a non-surgical therapeutic option.

8. Conclusion and Future Perspectives

Bromelain, a proteolytic enzyme complex from *A. comosus* (L.) Merr. demonstrates a compelling mechanistic basis for use in ocular disorders through its anti-inflammatory, antioxidant, proteolytic, and immunomodulatory actions. Preclinical studies reveal protective effects against oxidative and inflammatory damage to ocular tissues, as well as the ability to degrade vitreous collagen aggregates. Early clinical evidence, particularly from trials on mixed fruit enzyme formulations, supports its role in reducing symptomatic vitreous opacities and accelerating vitreous haemorrhage clearance, with an excellent safety profile.

However, the current evidence base remains preliminary. Isolating bromelain's individual contribution from multi-enzyme formulations, quantifying its ocular tissue bioavailability, and determining long-term safety in patients with compromised retinal integrity are essential next steps. Standardising bromelain preparations by proteolytic activity units (*e.g.*, GDU or MCU) will be critical for reproducibility across trials.

If validated by robust clinical trials, bromelain could emerge as a safe, cost-effective, and non-invasive adjunct or alternative to current surgical interventions for vitreous and retinal disorders, offering a novel addition to the ophthalmic therapeutic armamentarium.

9. References

1. Delaney YM, Oyinloye A, Benjamin L. Nd:YAG vitreolysis and pars plana vitrectomy: Surgical treatment for vitreous floaters. Eye (Lond). 2002; 16(1):21-26. https://doi.org/10.1038/sj.eye.6700026 PMid:11913884
2. Kokavec J, Wu Z, Sherwin JC, Ang AJ, Ang GS. Nd:YAG laser vitreolysis versus pars plana vitrectomy for vitreous floaters. Cochrane Database Syst Rev. 2017; 6(6):CD011676. https://doi.org/10.1002/14651858.CD011676.pub2 PMid:28570745 PMCid:PMC6481890
3. Kansakar U, Trimarco V, Manzi MV, Cervi E, Mone P, Santulli G. Exploring the therapeutic potential of bromelain: Applications, benefits, and mechanisms. Nutrients. 2024; 16(13):2060. https://doi.org/10.3390/nu16132060 PMid:38999808 PMCid:PMC11243481
4. Chakraborty AJ, Mitra S, Tallei TE, Tareq AM, Nainu F, Cicia D, *et al*. Bromelain a potential bioactive compound: A comprehensive overview from a pharmacological perspective. Life. 2021; 11(4):317. https://doi.org/10.3390/life11040317 PMid:33917319 PMCid:PMC8067380
5. Kumar V, Mangla B, Javed S, Ahsan W, Kumar P, Garg V, *et al*. Bromelain: A review of its mechanisms, pharmacological effects and potential applications. Food Funct. 2023; 14(18):8101-8128. https://doi.org/10.1039/d3fo01060k Erratum in: Food Funct. 2025; 16(16):6733. https://doi.org/10.1039/D5FO90061A PMid:40704392
6. Okkay IF, Okkay U, Bayram C, Cicek B, Sezen S, *et al*. Bromelain protects against cisplatin-induced ocular toxicity through mitigating oxidative stress and inflammation. Drug Chem Toxicol. 2023; 46(1):69-76. https://doi.org/10.1080/01480545.2021.2011308 PMid:34894956
7. Lin T, Li T, Zhang X, Hui Y, Moutari S, Pazo EE, *et al*. The efficacy and safety of YAG laser vitreolysis for symptomatic vitreous floaters of complete PVD or non-PVD. Ophthalmol Ther. 2022; 11(1):201-214. https://doi.org/10.1007/s40123-021-00422-6 PMid:34778916 PMCid:PMC8770727
8. Ma JW, Hung JL, Takeuchi M, Shieh PC, Horng CT. A new pharmacological vitreolysis through the supplement of mixed fruit enzymes for patients with ocular floaters or vitreous hemorrhage-induced floaters. J Clin Med. 2022; 11(22):6710. https://doi.org/10.3390/jcm11226710 PMid:36431188 PMCid:PMC9695351
9. Hammer M, Muuss M, Schickhardt S, Scheuerle A, Khoramnia R, Łabuz G, *et al*. Forward light scattering of the vitreous gel after enzymatic aging: An *in vitro* model to study vitreous opacification. Invest Ophthalmol Vis Sci. 2024; 65(3):36. https://doi.org/10.1167/iovs.65.3.36 PMid:38551585 PMCid:PMC10981431
10. Takeuchi M, Shieh PC, Horng CT. Treatment of symptomatic vitreous opacities with pharmacologic Vitreolysis using a mixture of bromelain, papain and ficin supplement. Appl Sci. 2020; 10(17):5901. https://doi.org/10.3390/app10175901
11. 11. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. Cell Mol Life Sci. 2001; 58(9):1234-1245. https://doi.org/10.1007/PL00000936 PMid:11577981 PMCid:PMC11337410
12. Pavan R, Jain S, Shraddha, Kumar A. Properties and therapeutic application of bromelain: A review. Biotechnol Res Int. 2012; 2012(1):976203. https://doi.org/10.1155/2012/976203 PMid:23304525 PMCid:PMC3529416
13. Pereira IC, Vieira EE, Torres LRd, da Silva FC, e Sousa JM, Torres-Leal FL. Bromelain supplementation and inflammatory markers: A systematic review of clinical trials. Clin Nutr ESPEN. 2023; 55:116-127. https://doi.org/10.1016/j.clnesp.2023.02.028 PMid:37202035
14. Beatty S, Koh HH, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol. 2000; 45(2):115-134. https://doi.org/10.1016/S0039-6257(00)00140-5 PMid:11033038
15. Kowluru RA, Chan PS. Oxidative stress and diabetic retinopathy. J Diabetes Res. 2007; 2007(1):043603. https://doi.org/10.1155/2007/43603 PMid:17641741 PMCid:PMC1880867
16. Secor Jr ER, Carson IV WF, Cloutier MM, Guernsey LA, Schramm CM, Wu CA, *et al*. Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murine model of allergic airway disease. Cell Immunol. 2005; 237(1):68-75. https://doi.org/10.1016/j.cellimm.2005.10.002 PMid:16337164 PMCid:PMC2576519
17. Nobre TA, de Sousa AA, Pereira IC, Pedrosa-Santos ÁMC, Lopes LD, Debia N, *et al*. Bromelain as a natural anti-inflammatory drug: A systematic review. Nat Prod Res. 2025; 39(5):1258-1271. https://doi.org/10.1080/14786419.2024.2342553 PMid:38676413
18. Milston R, Madigan MC, Sebag J. Vitreous floaters: Etiology, diagnostics, and management. Surv Ophthalmol. 2016; 61(2):211-227. https://doi.org/10.1016/j.survophthal.2015.11.008 PMid:26679984
19. Bhui K, Prasad S, George J, Shukla Y. Bromelain inhibits COX-2 expression by blocking the activation of MAPK regulated NF-kappa B against skin tumor-initiation triggering mitochondrial death pathway. Cancer Lett. 2009; 282(2):167-176. https://doi.org/10.1016/j.canlet.2009.03.003 PMid:19339108 PMCid:PMC11050791
20. Rathnavelu V, Alitheen NB, Sohila S, Kanagesan S, Ramesh R. Potential role of bromelain in clinical and therapeutic applications (Review). Biomed Rep. 2016; 5(3):283-288. https://doi.org/10.3892/br.2016.720 PMid:27602208 PMCid:PMC4998156
21. Pillai K, Akhter J, Chua TC, Morris DL. Anticancer property of bromelain with therapeutic potential in malignant peritoneal mesothelioma. Cancer Investig. 2013; 31(4):241-250. https://doi.org/10.3109/07357907.2013.784777 PMid:23570457

22. Taussig SJ. The mechanism of the physiological action of bromelain. Med Hypotheses. 1980; 6(1):99-104. https://doi.org/0.1016/0306-9877(80)90038-9 PMid:7382892 PMCid:PMC11050791
23. Paul S, Bhuyan S, Balasoupramanien DD, Palaniappan A. Muco-adhesive and muco-penetrative formulations for the oral delivery of insulin. ACS Omega. 2024; 9(23):24121-24141. https://doi.org/10.1021/acsomega.3c10305 PMid:38882129 PMCid:PMC11170654
24. Hosseinpour M, Dalband AM, Lajevardi Z, Soltanattar A, Tafazolimoghadam A, Karamian A, *et al*. The protective effect of bromelain on testicular dysfunction and oxidative stress induced by REM sleep deprivation in adult male rats. Tissue Cell. 2025; 95:102927. https://doi.org/10.1016/j.tice.2025.102927 PMid:40280068
25. White RR, Crawley FE, Vellini M, Rovati LA. Bioavailability of 125I bromelain after oral administration to rats. Biopharm Drug Dispos. 1988; 9(4):397-403. https://doi.org/10.1002/bod.2510090408 PMid:3207859
26. Castell JV, Friedrich GE, Kuhn CS, Poppe GE. Intestinal absorption of undegraded proteins in men: presence of bromelain in plasma after oral intake. Am J Physiol Gastrointest Liver Physiol. 1997; 273(1): G139-G146. https://doi.org/10.1152/ajpgi.1997.273.1.G139 PMid:9252520
27. Nazari A. Nutritional requirements for optimal surgical recovery. In: Handbook of oral and maxillofacial surgery and implantology, Cham: Springer Nature Switzerland; 2025. p. 1-78. https://doi.org/10.1007/978-3-031-36962-9_283-1 PMCid:PMC10956700
28. Irfan AA, Azkia A, Buhori A, Prabowo HA, Vania E, Adriani NH, *et al*. *In vitro* dissolution test of bromelain isolated from pineapple core encapsulated in hydrogel semi-IPN methyl cellulose-Chitosan. Proceedings of BROMO Conference BROMO - Volume 1; 2018. https://doi.org/10.5220/0009841700002406
29. 29. Zamboulis A, Nanaki S, Michailidou G, Koumentakou I, Lazaridou M, Ainali NM, *et al*. Chitosan and its derivatives for ocular delivery formulations: Recent advances and developments. Polymers. 2020; 12(7):1519. https://doi.org/10.3390/polym12071519 PMid:32650536 PMCid:PMC7407599
30. Ebrahimian M, Mahvelati F, Malaekeh-Nikouei B, Hashemi E, Oroojalian F, Hashemi M. Bromelain loaded lipid-polymer hybrid nanoparticles for oral delivery: Formulation and characterization. Appl Biochem Biotechnol. 2022; 194(8):3733-3748. https://doi.org/10.1007/s12010-022-03812-z PMid:35507250 PMCid:PMC9066387
31. Iacob AT, Lupascu FG, Apotrosoaei M, Vasincu IM, Tauser RG, Lupascu D, *et al*. Recent biomedical approaches for chitosan-based materials as drug delivery nanocarriers. Pharmaceutics. 2021; 13(4):587. https://doi.org/10.3390/pharmaceutics13040587 PMid:33924046 PMCid:PMC8073149
32. de Campos AM, Diebold Y, Carvalho EL, Sánchez A, Alonso MJ. Chitosan nanoparticles as new ocular drug delivery systems: *in vitro* stability, *in vivo* fate, and cellular toxicity. Pharm Res. 2004; 21(5):803-810. https://doi.org/10.1023/B:PHAM.0000026432.75781.cb PMid:15180338
33. Das S, Bhattacharyya D. Bromelain from pineapple: Its stability and therapeutic potentials. In: Bogsan CSB, Todorov S, editors. Tropical fruits: From cultivation to consumption and health benefits, pineapple, New York: Nova Science Publishers; 2017. p. 43-100.
34. Maheshwari S, Singh A, Wasim R, Prajapati BG, Malviya R, Shazly GA. Revealing the potential of mucoadhesive ocular nanoparticles for enhanced drug delivery. Curr Nanomed. 2025; 15(2):129-141. https://doi.org/10.2174/0124681873284203240328102643
35. Ross M, Sheardown L, Muirhead B, Mofford J, Tian J, Sheardown H. Mucoadhesive thermogel platform for treating anterior ocular conditions. J Biomed Mater Res A. 2023; 111(9):1390-1405. https://doi.org/10.1002/jbm.a.37541 PMid:37026843
36. Ashique S, Kumar P, Taj T, Debnath B, Mukherjee S, Patel A, *et al*. Nanotechnology: A state of the art for the management of ocular disorders-A roadmap. BioNanoScience. 2025; 15(2):285. https://doi.org/10.1007/s12668-025-01895-6
37. 37. Gorantla S, Rapalli VK, Waghule T, Singh PP, Dubey SK, Saha RN, *et al*. Nanocarriers for ocular drug delivery: Current status and translational opportunity. RSC Adv. 2020; 10(46):27835-27855. https://doi.org/10.1039/D0RA04971A PMid:35516960 PMCid:PMC9055630
38. Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. Prog Retin Eye Res. 2015; 49:67-81. https://doi.org/10.1016/j.preteyeres.2015.06.002 PMid:26113211 PMCid:PMC4651818
39. Schlunck G, Meyer-ter-Vehn T, Klink T, Grehn F. Conjunctival fibrosis following filtering glaucoma surgery. Exp Eye Res. 2016; 142:76-82. https://doi.org/10.1016/j.exer.2015.03.021 PMid:26675404
40. Aichele K, Bubel M, Deubel G, Pohlemann T, Oberringer M. Bromelain down-regulates myofibroblast differentiation in an *in vitro* wound healing assay. Naunyn Schmiedebergs Arch Pharmacol. 2013; 386(10):853-863. https://doi.org/10.1007/s00210-013-0890-z PMid:23771413
41. Ardeshiri H, Ghorbani M, Nazarinia MA, Falamarzi K, Tamaddon AM, Azarpira N. Niosomal hydrogel loaded with bromelain: a promising solution for reducing skin collagen in scleroderma patients. J Cell Mol Med. 2025; 29(14):e70478. https://doi.org/10.1111/jcmm.70478 PMid:40703002 PMCid:PMC12287664
42. Chen M, Li W, Du Y, Zhao Y, Guo Y, Li Y, *et al*. JAM-C prevents ocular fibrosis by suppressing the TAZ/KLF6 pathway. J Adv Res. 2026; 80:961-975. https://doi.org/10.1016/j.jare.2025.05.037 PMid:40398745 PMCid:PMC12869230

43. Jančič U, Gorgieva S. Bromelain and nisin: The natural antimicrobials with high potential in biomedicine. Pharmaceutics. 2021; 14(1):76. https://doi.org/10.3390/pharmaceutics14010076PMid:35056972 PMCid:PMC8778819
44. Fleiszig SM, Evans DJ. Pathogenesis of contact lens-associated microbial keratitis. Optom Vis Sci. 2010; 87(4):225-232. https://doi.org/10.1097/OPX.0b013e3181d408ee PMid:20190671 PMCid:PMC4379041
45. Rowan AD, Buttle DJ, Barrett AJ. The cysteine proteinases of the pineapple plant. Biochem J. 1990; 266(3):869-875.
46. Engwerda CR, Andrew D, Ladhams A, Mynott TL. Bromelain modulates T cell and B cell immune responses *in vitro* and *in vivo*. Cell Immunol. 2001; 210(1):66-75. https://doi.org/10.1006/cimm.2001.1807 PMid:11485354 PMCid:PMC11050791
47. Ma JW, Hung JL, Takeuchi M, Shieh PC, Horng CT. A new pharmacological vitreolysis through the supplement of mixed fruit enzymes for patients with ocular floaters or vitreous hemorrhage-induced floaters. J Clin Med. 2022; 11(22):6710. https://doi.org/10.3390/jcm11226710 PMid:36431188 PMCid:PMC9695351
48. Shah CP, Heier JS. YAG laser vitreolysis vs sham YAG vitreolysis for symptomatic vitreous floaters: A randomized clinical trial. JAMA Ophthalmol. 2017; 135(9):918-923. https://doi.org/10.1001/jamaophthalmol.2017.2388 PMid:28727887 PMCid:PMC5710539
49. Dysager DD, Koren SF, Grauslund J, Wied J, Subhi Y. Efficacy and safety of pars plana vitrectomy for primary symptomatic floaters: A systematic review with meta-analyses. Ophthalmol Ther. 2022;1 1(6):2225-2242. https://doi.org/10.1007/s40123-022-00578-9 PMid:36198880 PMCid:PMC9587141
50. de Nie KF, Crama N, Tilanus MA, Klevering BJ, Boon CJ. Pars plana vitrectomy for disturbing primary vitreous floaters: Clinical outcome and patient satisfaction. Graefes Arch Clin Exp Ophthalmol. 2013; 251(5):1373-1382. https://doi.org/10.1007/s00417-012-2205-3 PMid:23250478
51. Stalmans P, Benz MS, Gandorfer A, Kampik A, Girach A, Pakola S, *et al*. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. N Engl J Med. 2012; 367(7):606-615. https://doi.org/10.1056/NEJMoa1110823 PMid:22894573
52. Agrawal P, Nikhade P, Patel A, Mankar N, Sedani S, Nikhade PP. Bromelain: A potent phytomedicine. Cureus. 2022; 14(8):e27876. https://doi.org/10.7759/cureus.27876
53. Heitzig M, Linninger AA, Sin G, Gani R. A computer-aided framework for development, identification and management of physiologically-based pharmacokinetic models. Comput Chem Eng. 2014; 71:677-698. https://doi.org/ 10.1016/j.compchemeng.2014.07.016

Author Contributions

Conceptualisation, RDN and RM; investigation, RDN and RM; writing-original draft preparation, RDN, SP, OK, NP, and AS; writing-review and editing, RDN and RM. All authors have read and agreed to the published version of the manuscript.