International Journal of Otorhinolaryngology and Head and Neck Surgery
Srivastava A et al. Int J Otorhinolaryngol Head Neck Surg. 2022 Jul;8(7):621-627
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20221569

Review Article

Targeting the pathophysiology of chronic rhinosinusitis with systemic enzyme therapy: a narrative review

Amrita Srivastava[1]*, Vijay Shukla[2], Gautam V. Daftary[3]

[1]Department Otorhinolaryngology, Ganesh Shankar Vidyarthi Memorial (GSVM) Medical College, Kanpur, Uttar Pradesh, India
[2]Department of Otorhinolaryngology, Ajanta Hospital and IVF Centre, Lucknow, Uttar Pradesh, India
[3]Department of Research and Development, Aksigen Hospital Care, Mumbai, Maharashtra, India

Received: 18 May 2022
Revised: 01 June 2022
Accepted: 02 June 2022

***Correspondence:**
Dr. Amrita Srivastava,
E-mail: amritasri.gsvm@gmail.com

ABSTRACT

Chronic rhinosinusitis (CRS) is a prevalent condition with significant impact on quality of life and increases the economic burden. Medical treatment modalities for CRS are limited. Most of the drugs, currently in use, target mainly the symptomatology, rather than the pathophysiology of CRS. As more and more information become available, there is better understanding of the underlying mechanisms leading to CRS pathology. This also allows us to identify targets for therapy. The enzyme-flavonoid combination of trypsin-bromelain-rutoside appears to have multiple relevant mechanisms of action to counter some of the known major pathophysiological pathways in CRS. Taken together, the anti-inflammatory, anti-edema, fibrinolytic, vasoprotective and antioxidant actions of the combination can be beneficial in the management of CRS. The literature evidence of these mechanisms, few relevant clinical studies and their potential to benefit CRS therapy has been discussed in this narrative review.

Keywords: Sinusitis, Inflammation, Trypsin, Bromelain, Rutoside

INTRODUCTION

Sinusitis is a common term for inflammation of the mucosal lining of nasal and paranasal cavities. Due to the involvement of inflammation of nasal mucosa it is also referred to as rhinosinusitis.[1-3] Rhinosinusitis can be classified into four types based on duration of persistence of symptoms-acute, subacute, recurrent acute and CRS. CRS is characterized by a combination of sinus pressure, anosmia, mucopurulent nasal drainage, and nasal congestion for greater than 12 weeks.[4] Other associated symptoms include facial pain and fullness, headache, toothache, fever or malaise and halitosis.[2,3,5,6] These symptoms, however, are non-specific and for a definitive diagnosis, evaluation by nasal endoscopy or computed tomography (CT) imaging is often required.[7] CRS is further classified as chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). CRS is often initiated by infection, allergy or autoimmunity.[1]

CRS significantly impacts the quality of life and is associated with economic burden due to recurrent nature of condition, repeated use of over-the-counter medications and loss of wages because of missed days from work. It has been estimated that the direct and indirect costs associated with CRS add up to 8.3 billion US dollars annually.[7] The global prevalence of CRS is estimated at 11-12% and in Asia it is 2.2-10.8%.[8,9] According to national institute of allergy and infectious diseases (NIAID) figures, India is greatly afflicted by CRS with about 134 million Indians suffering from CRS.

It is estimated that one in eight Indians suffer from chronic sinusitis.[10] According to a study carried out at Government Unani Hospital Srinagar and AYUSH centers of Kashmir division in India, 34 years was estimated mean age of sinusitis patients.[6]

CURRENT TREATMENT MODALITIES

Symptomatic relief remains the major goal of treatment in CRS. Humidification, saline nasal irrigation, rest and hydration are some of the primary recommendations to relieve symptoms. Decongestants (topical or systemic) are also frequently used.[1,5,11] Steroids, topical and systemic, help in diminishing nasal mucosal edema.[5,12] Antibiotics are resorted to, in case of persistent or worsening of symptoms and failure to respond to initial intranasal steroid therapy. Often, drugs like amoxicillin-clavulanate are used as first line antibiotic treatment when symptoms do not improve. Other classes of antibiotics include cephalosporins, macrolides, clindamycin and fluoroquinolones.[1,3,5] Sinus surgery is the option for patients who do not benefit with medication. In endoscopic sinus surgery, soft tissue obstructing the natural drainage ostia, nasal polyps and inflammatory tissue get removed in an attempt to restore sinus ventilation, drainage and mucociliary function.[1,3,11] Over-the-counter (OTC) analgesics, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen are also commonly used.[12] Despite these therapies, CRS remains a challenging condition to treat. Targeting underlying immune and inflammatory mechanisms may prove more efficient in management of CRS.

PATHOPHYSIOLOGY OF INFLAMMATION IN CRS

CRS, although a very prevalent condition, remains poorly understood in terms of its pathophysiology. It is widely accepted that multiple diverse factors are involved in its trigger and further course of persistent inflammation. Research in this field indicate a complex interplay of environmental triggers and the innate and adaptive immune mechanisms in the body. Dysregulated persistent inflammation caused by this interplay is believed to be at the center of CRS.[4,13] Despite the complexity there are some broad common pathways that can be attributed to the pathophysiology of inflammation in CRS and serve as targets for treatment. These have been elucidated further.

Healthy sinuses are characterized by the presence of commensal bacterial species and strong epithelial tight junctions. However, the lining epithelium is constantly exposed to the environmental pathogens and particulates. The epithelial cells recognize molecular patterns (both pathogen-associated and damage-associated molecular patterns-PAMPs and DAMPs) via pattern recognition receptors (PRRs) located both on the cell surface and in intracellular endosomes.[4,7,13] The activation of PRRs initiates both local secretion of antimicrobial substances and production of signaling molecules for the innate immune response. These further activate the transcription factors like nuclear factor kappa B (NF-κB), and interferon response factors that activate transcription of antimicrobial peptides (AMPs), cytokines, and chemokines. These cytokines and interferons serve as a link to further adaptive immune responses, which start with the recruitment of dedicated immune cells, while also communicating with resident cell types like dendritic cells. Although these processes exist to protect the host, inappropriate activation or lack of inhibition leads to disruption of homeostasis and chronic inflammation. [4,7,13]

In CRSsNP, the immune cells predominantly comprise of neutrophils and macrophages that get recruited under the influence of chemokines like IL-8, MIP-1 (macrophage inflammatory protein-1), MCP-1 (monocyte chemoattractant protein-1) and RANTES (regulated on activation, normal T cell expressed and secreted).[13] CRSwNP has a different inflammatory profile-the type 2 inflammatory environment, believed to be driven by a different set of cytokines that includes IL-4, IL-5, and IL-13. The cells that dominate such inflammation are eosinophils, basophils, and mast cells.[7,14] The macrophages further differentiate into M1 and M2 phenotypes. The M1 macrophages produce proinflammatory cytokines, phagocytize microbes, and produce reactive oxygen species and reactive nitrogen species. The M2 macrophages produce either polyamines or proline and are associated with wound healing and tissue repair. T cells also play a major role in the adaptive immune processes and serve to activate M1 macrophages, while additionally releasing more inflammatory cytokines like IFN-γ, IL-2, IL-4, IL-5, IL-13, IL-17, IL-22, TGF-β.[11] Cytokines like IL-6 lead to increased vascular permeability, followed by fibrin deposition and cross-linking; this is especially relevant in CRSwNP.[4] Most of these mediators, if remain unchecked, lead to state of self-perpetuating and persistent inflammation.

SYSTEMIC ENZYME THERAPY

Systemic enzyme therapy (SET), involving the oral administration of a combination of proteolytic enzymes and flavonoids, has been used since decades due to its therapeutic properties such as anti-inflammatory, analgesic actions, anti-edematous, antioxidant and antithrombotic effects. In India one such combination, of trypsin, bromelain and rutoside, is available in the forms of dispersible tablets (example-Disperzyme) and enteric-coated tablets (example-Phlogam). Advances in analytical techniques in the field of biology have led to better understanding of the mechanisms of action of the individual ingredients in this therapy. SET is effective in both, acute and chronic inflammatory conditions and can be used alone or as adjuvant to conventional treatment modalities. The relevant mechanisms by which the individual components act and can potentially benefit in CRS management have been elucidated further.

TRYPSIN-MECHANISMS

Trypsin, an animal-derived serine protease enzyme, has been known to possess fibrinolytic, anti-inflammatory and immunomodulating properties.[15] These effects have been demonstrated to be primarily mediated by its action on plasmin, T cells and M2 macrophages.

Trypsin circulates in bloodstream bound to plasma proteins, to which plasmin also binds. In the presence of more trypsin, the protein-bound plasmin is competitively displaced allowing more free plasmin to be available for fibrinolysis. The fibrinolytic effects of trypsin have been demonstrated in experimentally produced thrombi in rabbits and dogs, wherein it led to reduction of *in situ* thrombus, local circulation restoration, and restoration of vessel wall compressibility. There was reduction in cellular and platelet masses and fibrin.[16] Fibrin breakdown ultimately results in removal of inflammatory products and adequate supply of oxygen and nutrients to improve macro and micro-circulation.[17] *In vitro* studies have also demonstrated that when fibrinogen was exposed trypsin, it reduced the ability of thrombin to form fibrin clots.[18]

Trypsin modulates the threshold of T-cell activation by antigen-presenting cells (APCs) without impacting cell viability; this has been demonstrated in both *in vitro* and *in vivo* studies. Accessory molecules on APC were selectively cleaved by trypsin, thereby modulating the activation threshold for T cells.[19,20] This was mediated by cleavage of three cell surface molecules central for regulating T-cell activation threshold.

Trypsin also aids in tissue repair by its effect on macrophage differentiation. This effect was demonstrated in peripheral blood mononuclear cells (PBMCs) and monocytes. The differentiation of human monocytes to fibrocytes in cell culture was found to be potentiated by trypsin. Macrophages, when treated with trypsin, were altered toward an M2a phenotype, both in terms of their surface marker expression and secretion profile; these cells are involved in wound healing and fibrosis. This effect of trypsin was mediated through protease activated receptor (PAR)1 and PAR2 receptors.[21] Trypsin, also, effectively decreases interleukin (IL)-8-induced neutrophil migration to sites of acute inflammation both *in vitro* and *in vivo*.[22]

BROMELAIN-MECHANISMS

Bromelain is a group of cysteine proteases obtained from the fruit or stem of the pineapple plant. It possesses anti-inflammatory, anti-edematous and fibrinolytic properties; these have been demonstrated to be mediated by its effects on T cell signalling, leucocyte migration, bradykinin, and plasminogen.[23,24]

Bromelain inhibits T cell signalling and cytokine production by blocking the activation of extracellular regulated kinase-2 (ERK-2) in T cells.[25] Bromelain led to a significant shift in the circadian profiles of the Th1 cell mediator IFN-γ and trends in those of the Th2-type cytokine IL-5 and immunosuppressive cytokine interleukin (IL)-10.[26]

In an *in vitro* leukocyte migration assay, bromelain was able to reduce migration of human neutrophils in response to IL-8 by 40%. This was further confirmed in 3 murine models, in which a 50-85% reduction in neutrophil migration was observed with bromelain treatment. Bromelain treatment, through intravital microscopy, was found to decrease leukocyte rolling and reverse the firm adhesion of leukocytes to blood vessels at the inflammation site.[22] The underlying mechanism was demonstrated in an *in vitro* study on whole blood, in which bromelain proteolytically altered 14 of 59 leukocyte cell surface markers; the altered molecules were those which are involved in leukocyte homing, cellular adhesion, and activation.[27]

Bradykinin, a peptide that mediates vasodilation, increased capillary permeability and synthesis of other proinflammatory agents like prostaglandins, leukotrienes, histamine, endothelium-derived relaxing factor etc., is depleted from plasma by bromelain. This is achieved by the reduction of pre-kallikrein and high-molecular-weight (HMW) kininogen.[23,28] This has further been demonstrated in carrageenan-induced, kininogen-potentiated, rat paw edema model, where intravenous injection of bromelain reduced the levels of plasma kininogen and led to suppression of edema.[29]

Bromelain causes fibrinolysis by stimulating the conversion of plasminogen to plasmin, as demonstrated *in vitro* and *in vivo*.[30] It led to a 0.8 to 2.5 times increase in the prothrombin time and antithrombin time, with elevation of serum plasmin levels when administered orally to rabbits.[23] Similar findings were observed in rats.[23] The fibrinolytic activity is further complemented by its anti-platelet effect which has been demonstrated on isolated human platelets, *in vitro* by Coulter counter measurements.[31]

The impact of bromelain on arachidonic acid metabolism has been established in studies. Prostaglandin E2 and thromboxane B2 levels in rats are reduced by bromelain in a dose-dependent manner in experimentally induced inflammation models.[23] After oral *in vivo* administration in rats with carrageenin-induced inflammation, bromelain led to significant decrease of both PGE2 and substance P concentrations in the exudate.[32] The anti-inflammatory, and proteolytic effects of bromelain were demonstrated by evaluation of macroscopic and histopathologic scores in rat model of intra-abdominal adhesions.[33] Enhanced absorption and tissue penetration of antibiotics, without hampering the safety profile is also a feature of bromelain.[34]

RUTOSIDE-MECHANISMS

Rutoside is a bioflavonoid glycoside, extracted largely from citrus fruits like lemons, oranges, grapes, berries, limes, and peaches. It has anti-inflammatory, antioxidant and vasoprotective properties.[35,36] These activities are mediated by its effects on NF-κB, gene transcription in macrophages, and reactive oxygen as well as nitrogen species.

In an *in vitro* lipopolysaccharide (LPS)-induced inflammation model with mouse muscle cells, rutoside were found to significantly block NF-κB activation and LPS-induced ROS production. This was accompanied by attenuation of LPS-induced TNF-α and iNOS gene expression, and lower levels of IL-6 mRNA.[37] In human macrophages, more than 20 genes encoding critical pro-inflammatory factors, including IL-1, IL-8, TNF-α, macrophage migration inhibitory factor, and chemotactic factors were found to be inhibited by rutoside.[38] These findings were further corroborated in animal model studies, in which rutoside led to modulation of apoptosis and cell cycle, reduced the levels of ROS, calpain, and ceramide, decreased significantly, TNF-α, IL-1β, the p53 activities, and mitogen-activated protein kinase phosphorylation in the kidneys, reduced levels protein of Bax, and increased the levels of Bcl-2 protein.[39]

The free radical scavenging and chelating activity of rutoside has been demonstrated in rat liver microsomes, wherein superoxide ions, hydroxyl radicals, and lipid peroxy radicals were found to be markedly reduced by rutoside.[40] In human activated macrophages, inducible nitric oxide synthase (iNOS)-mediated NO production was also decreased in a dose-dependent manner.[38] In an LPS-induced acute kidney injury model in mice, rutoside restored the oxidative stress-related indices such as glutathione, malondialdehyde, and activity of superoxide dismutase and catalase. Similar effects were observed in the levels of toll-like receptor 4, renal NF-κB, cyclooxygenase-2 (COX2), TNF-α, IL-6, sirtuin 1 (SIRT1), and caspase 3 activity.[41] It has also been demonstrated to prevent peroxide-induced apoptosis of human umbilical vein endothelial cells through regulating ROS-mediated mitochondrial dysfunction pathway as well as protects the intracellular the GSH antioxidant system.[42]

The reduction of NO due to inhibition of iNOS by rutoside, described earlier, and further evidence of reduction of histamine-, bradykinin and fibrin degradation products (FDP)- induced microvascular permeability in rat skin model and frog mesentery capillaries, demonstrates the vasoprotective action of rutoside.[43,44] This is further complemented by its anti-platelet action, resulting from inhibition of intracellular Ca2+ mobilization, reduced serotonin (5-HT) release and inhibition of thromboxane A2 formation.[45,46]

The primary mechanisms by which the individual components of the trypsin-bromelain-rutoside combination can target the pathophysiology of CRS have been summarized in Figure 1.

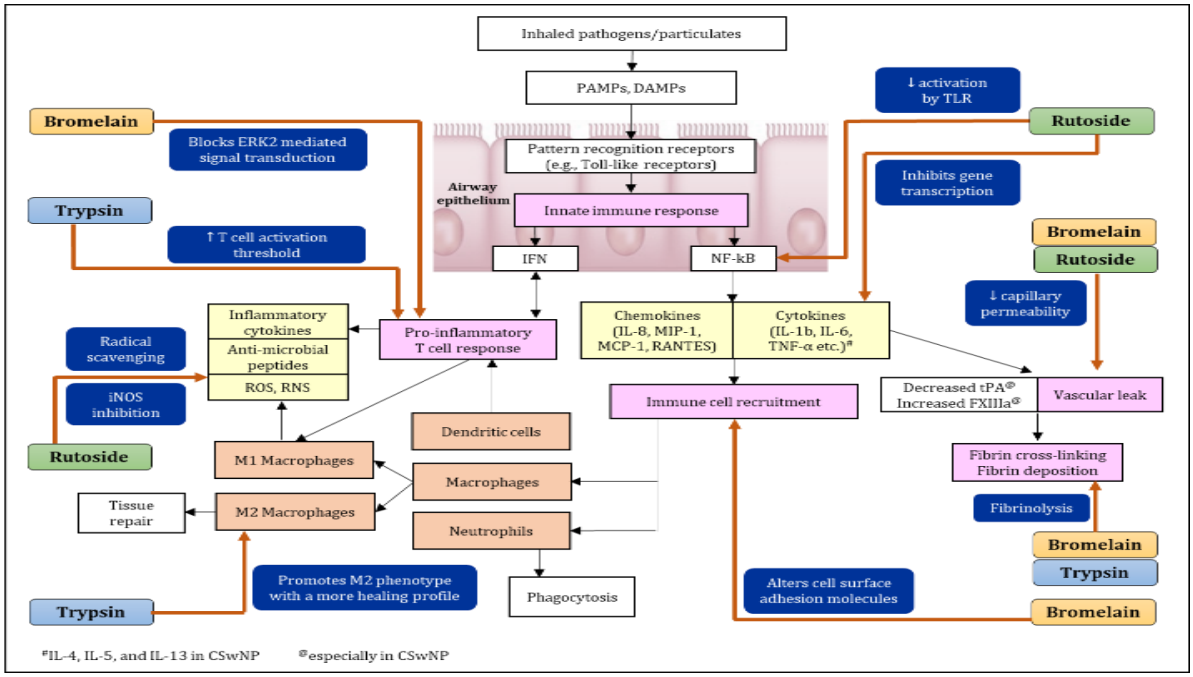

Figure 1: Targets of trypsin, bromelain and rutoside in the pathophysiology of chronic rhinosinusitis.

PAMP-pathogen-associated molecular pattern (lipoprotein, lipopolysaccharide, flagellin etc.), DAMP-damage-associated molecular pattern (high-mobility group box 1, DNA, RNA etc.), IFN-interferon (gamma), NF-κB-nuclear factor-kappa B, IL-interleukin, RANTES-regulated on activation, normal T cell expressed and secreted, MIP-1-macrophage inflammatory protein-1, MCP-1-monocyte chemoattractant protein-1, TNF-tumour necrosis factor, tPA-tissue plasminogen activator, ERK2-extracellular signal-regulated kinase 2, ROS- reactive oxygen species, RNS-reactive nitrogen species, iNOS-inducible nitric oxide synthase.

CLINICAL EVIDENCE

Some clinical trials have been conducted to evaluate safety and efficacy of proteolytic enzymes and their combinations with respect to relief in various forms of sinusitis and associated conditions.

Some of the earliest studies, from the 1960s, found that bromelain treatment was beneficial in patients of both acute and chronic sinusitis. Three separate randomized, controlled trials found that it reduced symptoms of CRS.[47-49] Among these, in a double-blind placebo-controlled study of patients with sinusitis who were not treated with antibiotics, bromelain led to compete resolution of nasal mucosal inflammation and breathing difficulties in 85% of the recipients. On the other hand, only 40% and 53% in the placebo group had resolution of inflammation and breathing difficulties, respectively.[48]

The anti-inflammatory action of systemic enzyme-flavonoid combination in sinusitis was evaluated in a randomized, double-blind, and parallel group study in comparison with diclofenac (an NSAID often recommended for sinusitis). In this study, 40 patients were distributed in two groups. One teaspoon of a granulated compound containing bromelain, papain, pancreatin, trypsin and chymotrypsin plus the bioflavonoid rutin, and two placebo capsules were given to one group twice daily, while the other group received granulated placebo and capsules of diclofenac twice daily for 14 days. Patients in both groups showed similar improvement in headache and toothache, but the enzyme-treated group showed better tolerability.[50]

More recently, bromelain was evaluated in acute sinusitis patients under the age of 11 years. Children were distributed in three treatment groups-62 patients treated with bromelain only, 34 patients treated with a combination of bromelain and standard therapy, and 20 patients treated with standard therapy only. The bromelain monotherapy group showed significantly faster recovery from symptoms. No side effect were observed except for one patient, with known history of pineapple allergy, reporting a self-limiting mild allergy.[51]

One observational pilot study was conducted to observe the efficacy and tolerability of bromelain tablet treatment and its impact on QoL in patients with CRS and acute swelling after sinus surgery in clinical practice. Twelve patients suffering from CRSwNP or CRSsNP who had undergone prior sinus surgery were treated with bromelain tablets for three months. Symptom scores, rhinoscopy scores and quality of life was assessed, and improvement observed with bromelain treatment. Also, good tolerability observed as there weas no reported adverse event.[52]

Trypsin, administered via mouth spray, was evaluated in a randomized, double-blind, placebo-controlled study on 46 healthy volunteers inoculated with rhinovirus 16 via the nose. The trypsin spray treatment resulted in a lower total viral load in the oropharynx and lesser number of days with common cold symptoms (6.5 vs 3.0 days), in comparison to placebo.[53]

Rutosides have also been evaluated for similar indications, based on their potential to reduce capillary permeability and edema. In an active-controlled study, troxerutin, one of the rutosides, was given in combination with zinc gluconate to 49 patients with common cold symptoms and compared against 45 patients who received only zinc gluconate. Over 4 days of treatment, symptoms were scored, and it was identified that there was significant reduction in rhinorrhea in the rutoside group over the course of the study.[54]

Flavonoids like rutosides have also been extensively evaluated in the treatment of viral acute respiratory tract infections, which often serve as triggers for CRS. A recently published meta-analysis reported that in common cold, flavonoids decreased the total cold intensity score and the duration of inability to work vs. the control group. Similar results were reported in patients of acute non-streptococcal tonsillopharyngitis, acute rhinosinusitis and acute bronchitis. In bronchial pneumonia, the improvement with flavonoids was accompanied by reporting of reduced levels of IL-6, IL-8, and TNF-α. Adverse events incidence was similar to the control group.[55]

CONCLUSION

CRS is a widely prevalent condition with an obscure and potentially heterogenous and complex pathophysiology. Current treatment strategies are limited with primary focus of therapy being symptomatic relief. An increasing body of evidence indicates that the enzyme-flavonoid combination of trypsin, bromelain and rutoside can target many of the known pathways in the inflammatory pathology of CRS, thereby helping in physiological recovery. This, along with the history of decades of safe use of these natural ingredients, make them a very attractive option for the management of CRS.

Funding: No funding sources
Conflict of interest: Daftary GV is the chairperson of Aksigen Hospital Care Limited, which markets a few brands of systemic enzymes in India
Ethical approval: Not required

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Cite this article as: Srivastava A, Shukla V, Daftary GV. Targeting the pathophysiology of chronic rhinosinusitis with systemic enzyme therapy: a narrative review. Int J Otorhinolaryngol Head Neck Surg 2022;8:621-7.