

Journal of Otolaryngology Forecast

Application of Bromelain and Proteases in Otolaryngology Practice

Murray Grossan*

Otolaryngologist, Tower, Ear, Nose and Throat, USA

Introduction

Bromelain is a proteolytic enzyme from pineapple and pineapple stems. The purpose of this report is to discuss my experience using these products in my Otolaryngology practice.

The application of Bromelain in ENT can be significant due to its properties:

- Reduces pain
- Anti-inflammatory effect
- Reduction of swelling
- Increases absorption of drugs
- Use in trauma
- Application to Eustachian tube blockage
- Application to Sinus Blockage
- Reduction of thickness of mucus

My personal experience with Bromelain began with the protease Papain which was available as a buccal tablet. Papain is an enzyme extracted from papaya. Culturally, natives wrap papaya leaves around wounds. I found Papain easy to use for reducing many forms of swelling and ear blockage.

When the buccal Papain was no longer available, I had to have a combination of Bromelain, Protease and Papain compounded for me for buccal use [1-3].

The peer reviewed double blind studies are noticeably missing here. Bromelain is an Herbal Remedy used by herbalist, naturopaths, etc. It is OTC, inexpensive and easily produced. Since it cannot be patented, there haven't been funds available for peer reviewed evaluations. In addition, sometimes outlandish claims have been made by some producers that prompted governments to close those companies. I hope, by this recount of my personal experience, these barriers can be overcome.

Eustachian Tube Obstruction (ETO)

As an advanced scuba diver, I have taken courses in scuba medicine. Eustachian blockage is the primary reason why many persons are unable to scuba dive. By coincidence, my office at that time was a short distance from Los Angeles International Airport. This location funneled pilots, fliers and divers to my office, primarily with ear complaints. The experience of 25 years of daily use of Bromelain, certainly indicates the value of Bromelain for Eustachian Tube Obstruction.

For persons with a history of difficulty in clearing their ear for diving or altitude changes, the nasopharynx is examined as well as the nose and sinus openings. In the absence of obstructive pathology, these patients were placed on the Bromelain/Papain combination. Because there were few failures, this method of treatment has been a cornerstone of my therapy. Because there are essentially no side effects, patients take a full day's medication the day before they dive or fly and continue them during the dive excursion. This product is safe to use in deep dives where the pressure may be 4x that of the ground atmosphere, as well as in altitude changes.

There are various procedures available used for dilatation of the eustachian tube. Since Bromelain is available and has been shown to be effective for ETO, it would be valuable to do a trial of Bromelain to test its ability to clear the blockage. Perhaps using Bromelain would make surgery unnecessary.

OPEN ACCESS

***Correspondence:**

Murray Grossan, Otolaryngologist,
Tower, Ear, Nose and Throat, USA.

E-mail: drgrossan@yahoo.com

Received Date: 27 May 2018

Accepted Date: 20 Jul 2018

Published Date: 23 Jul 2018

Citation: Grossan M. Application of Bromelain and Proteases in Otolaryngology Practice. *J Otolaryngol Forecast.* 2018; 1(1): 1007.

Copyright © 2018 Murray Grossan.

This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Side Effects

Regarding side effects

Patients who are allergic to pineapple, do show allergy to Bromelain. Approximately 4% of patients find the buccal route irritating. They are switched to taking it via oral route with water before meals. It is important to emphasize buccal route and not sublingual. Sublingual tissue is too thin to administer such a strong enzyme [4].

Vacuum sinusitis

I have treated persons who land at the airport and have severe pain in the sinus areas. These patients are seen as an emergency, since the pain is severe. The sinus openings are vasoconstricted with packs, and then the patients are maintained on the Bromelain/Papain combination.

Sinusitis

Several references listed here are of studies showing increased permeability of tissue to antibiotics using Bromelain. In sinusitis, the period of duration of antibiotic therapy is longer than for bronchitis because the antibiotic must reach areas of bacteria with poor vascular access, such as a 3ml pool of infected material in the maxillary sinus. Therefore, I often add the Bromelain to the therapy in difficult cases.

The property of Bromelain to shrink swollen tissues, is of particular benefit in Sinusitis, and may even improve sinus cavity blockage, as it does the Eustachian tube [5-9].

Post trauma swelling

The ENT doctor sees traumatic injuries all the time. Speed at reduction of this swelling is needed. The following reports have studied the actions of Bromelain on trauma, and are fair indications for its use. With the added benefits of low cost and minimal side effects, I would recommend using Bromelain for trauma. In one study, boxers were placed on Bromelain with measured reduction of post trauma swelling and hematoma [7,10,11].

The Uvula

When the uvula is swollen, whether from trauma, allergy or infection, the patient's symptoms are severe, including difficulty of swallowing, sensation of air blockage, and pain. Because the action of bromelain is to reduce swelling, this has been my therapy for such cases, in addition to systemic medications and corticosteroids.

Adenoidectomy

One of the primary reasons for adenoid surgery is eustachian blockage and recurrent middle ear infections. However, there are certain patients where surgery might be avoided. Or, the parents are set against any surgery, and insist on some other approach. I have placed these children on Bromelain in order to attempt to shrink the inflammatory aspect of the adenoids. I cannot say what % of these cases were successful, but it remains an avenue to consider.

Debridement of Burns and Wounds

Literature here is well documented and certainly should be considered in such cases. The studies include laboratory experimental studies, as well as actual patient debridement in wounds, burns, and tissue traumas. It is also used topically in a cream – 35% in a suitable base [12-15].

Temporomandibular Joint Disorders -TMJD

The otolaryngologist sees patients whose complaint of ear pain is due to the TMJ. Often, they have seen other doctors, who stated that there was no ear infection and recommended pain pills. Several careful studies have been done on using Bromelain for acute rheumatoid arthritis and swollen joints. Since Bromelain has been studied extensively for its role in joint symptoms, I have encouraged its use for TMJD. It does work, along with instructions on using mirror biofeedback to learn jaw relaxation and opening the jaw midline by following a vertical line on the mirror. This method is particularly useful for patients who grind their teeth at night, damage their teeth, and keep their partner awake. However, there is no evidence that it is more effective than dental or other methods.

Patients who have been prescribed Bromelain/Papain for other purposes, such as ETO, have often remarked that they had a reduction in joint pains, and asked if they could use it for that purpose.

Cancer Inflammation

I have read articles addressing use of Bromelain in inflammation related to cancer. I have added some references that should be reviewed and considered for further research [16-19].

Bromelain vs Corticosteroids

The actions of corticosteroids have been studied thoroughly, including the application for swelling and inflammation. The applications of Bromelain have not had such extensive clinical investigations.

I have told this to my patients and explained that as far as is known, corticosteroids are superior. However, because of minimal side effects I have preferred to use the proteolytic enzyme route first, if possible. An advantage of using Bromelain is that it can be used for long periods of time without supervision.

Oral vs Buccal

The literature has studied the absorption of Bromelain from stomach and intestines, and has shown excellent absorption when taken without food. I find that patients do well via buccal pouch. It is my belief that there is better absorption. It would certainly be of value to perform a study to evaluate if buccal is superior to oral use [20,21].

Joint Swelling

The literature reports favorable results with Bromelain for various kinds of joint swelling. Similar applications in Otolaryngology should be considered. My experience with using Bromelain for TMJD has been positive. Cervical and arytenoid use may be of value. Certainly a careful study is indicated here [22-25].

Voice

Since I practice in the land of Hollywood, hoarseness and voice changes are of paramount importance to my patients. My experience with performers would strongly indicate that Bromelain is a primary aid for hoarseness due to excessive vocal use. My performers often carry a package of the Bromelain/Papain combination with them when they travel, in case they should develop signs of hoarseness.

Pure Bromelain vs Combinations

I have chosen to use a combination of Bromelain with Papain.

However, research has been primarily in pure Bromelain and I know of no studies comparing Bromelain itself vs combinations. I believe the important factor is that the enzymatic activity be stated for each tablet so that the doctor can decide on the medication. Papain has been studied as an aid to reduce pain [26].

Reported Medicinal Uses

There are reports in the literature of beneficial effects in angina pectoris, transient ischemic attacks, prevention and treatment of thrombophlebitis, dissolving cholesterol plaques, and for fibrinolytic action. Also it has been reported useful in skeletal muscular injuries.. There is extensive literature on its use in Rheumatic Osteoarthritis [27].

There are various mechanisms described for Bromelain's action. It inhibits T cell signal transduction, it decreases CD4 T cells, and reduces the expression of CD25.

The fact that Bromelain is effective in Rheumatoid Arthritis, indicates it has value in an autoimmune condition, and should be explored in other ones.

Discussion

The studies of the mechanisms of Bromelain indicate other applications that are outside of ENT practice. For example, the effect of Bromelain on inflammation in cases of Type 1 diabetes have been dramatic. I would invite readers to the listed articles for review [27-50].

My practice has relied on,

Bromelain 1,000,000 FCCPU units,

Papain 500,000 FCCPU units,

Protease 8,750 HUT units,

There are other units of enzyme measurement that are used including FIP units. These analyze based on enzymatic activity on various substrates. A common measure is GDU – measure of action on gelatin. Thus, the grams of Bromelain are not a good measure; it is the measure of enzymatic activity that is significant [51-59].

Whether a Papain/Bromelain formula has advantage over others is not established here. What is important is that Bromelain has been studied with evidence of benefits, is available world- wide, is inexpensive, with few side effects. On the other hand, eustachian tube blockage, swollen joints, infected sinuses are prevalent world- wide, and Bromelain offers an approach to be considered [60-69].

References

- Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cellular and Molecular Life Sciences*. 2001; 58: 1234–1245.
- Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application. An update. *J Ethnopharmacol*. 1988; 22: 191–203.
- Pavan R, Jain S, Shradha, Kumar A. Properties and therapeutic application of bromelain: a review. *Biotechnol Res Int*. 2012; 2012: 976203.
- Moss JN, Frazier CV, Martin GJ. Bromelains. The pharmacology of the enzymes. *Arch Int Pharmacodyn Ther*. 1963; 145: 166–189.
- Neubauer RA. A plant protease for potentiation of and possible replacement of antibiotics. *Experimental Medicine and Surgery*. 1961; 19: 143–146.
- Bodi T. The effects of oral bromelains on tissue permeability to antibiotics and pain response to bradykinin: double blind studies on human subjects. *Clinical Medicine*. 1966; 73: 61–65.
- Kumakura S, Yamashita M, Tsurufuji S. Effect of bromelain on kaolin-induced inflammation in rats. *Eur J Pharmacol*. 1988; 150: 295–301.
- Mynott TL, Ladhams A, Scarmato P, Engwerda CR. Bromelain, from pineapple stems, proteolytically blocks activation of extracellular regulated kinase-2 in T cells. *Journal of Immunology*. 1999; 163: 2568–2575.
- Guo R, Canter PH, Ernst E. Herbal medicines for the treatment of rhinosinusitis: a systematic review. *Otolaryng Head Neck*. 2006; 135: 496–506.
- Taussig SJ, Yokoyama MM, Chinen A, Onari K, Yamakido M. Bromelain: a proteolytic enzyme and its clinical application. A review. *Hiroshima J Med Sci*. 1975; 24: 185–193.
- Tassman GC, Zafran JN, Zayon GM. A double-blind crossover study of a plant proteolytic enzyme in oral surgery. *The Journal of Dental Medicine*. 1965; 20: 51–54.
- Houck JC, Chang CM, Klein G. Isolation of an effective debriding agent from the stems of pineapple plants. *International Journal of Tissue Reactions*. 1983; 5: 125–134.
- Rosenberg L, Kriehar Y, Silverstain E, et al. Selectivity of a Bromelain Based Enzymatic Debridement Agent: A Porcine Study. Elsevier. 2012.
- Singer AJ, McClain SA, Taira BR, Rooney J, Steinhaff N, Rosenberg L. Rapid and selective enzymatic debridement of porcine comb burns with bromelain-derived Debrase: acute-phase preservation of noninjured tissue and zone of stasis. *Journal of Burn Care and Research*. 2010; 31: 304–309.
- Wu SY, Hu W, Zhang B, Liu S, Wang JM, Wang AM. Bromelain ameliorates the wound microenvironment and improves the healing of firearm wounds. *Journal of Surgical Research*. 2012; 176: 503–509.
- Tysnes BB, Maurer HR, Porwol T, Probst B, Bjerkgvig R, Hoover F. Bromelain reversibly inhibits invasive properties of glioma cells. *Neoplasia*. 2001; 3: 469–479.
- Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008; 454: 436–444.
- 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: 167–176.
- Bhui K, Tyagi S, Srivastava AK, Singh M, Roy P, Singh R, et al. Bromelain inhibits nuclear factor kappa-B translocation, driving human epidermoid carcinoma A431 and melanoma A375 cells through G2/M arrest to apoptosis. *Mol Carcinogen*. 2012; 51: 231–243.
- Castell JV, Friedrich G, Kuhn CS, Poppe GE. Intestinal absorption of undegraded proteins in men: presence of bromelain in plasma after oral intake. *Am J Physiol-Gastr L*. 1997; 273: G139–G146.
- Seifert J, Ganser R, Brendel W. Absorption of a proteolytic-enzyme originating from plants out of the gastrointestinal-tract into blood and lymph of rats. *Z Gastroenterol*. 1979; 17: 1–8.
- Cohen A, Goldman J. Bromelains therapy in rheumatoid arthritis. *Pennsylvania Med J*. 1964; 67: 27–30.
- Hale LP, Greer PK, Sempowski GD. Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. *Clin Immunol*. 2002; 104: 183–190.
- Hale LP, Greer PK, Trinh CT, Gottfried AR. Treatment with oral bromelain decreases colonic inflammation in the IL-10-deficient murine model of inflammatory bowel disease. *Clin Immunol*. 2005; 116: 135–142.
- Leipner J, Iten F, Saller R. Therapy with proteolytic enzymes in rheumatic disorders. *Bio Drugs*. 2002; 15: 779–789.

26. Cooreman W. Bromelain. In: Ruysen R, Lauwers A, editors. *Pharmaceutical Enzymes- Properties and Assay Methods*. Gent, Belgium: E. Story-Scientia Scientific Publishing Co. 1978: 107–121.
27. Neumayer C, Fügl A, Nanobashvili J, et al. Combined enzymatic and antioxidative treatment reduces ischemia-reperfusion injury in rabbit skeletal muscle. *Journal of Surgical Research*. 2006; 133: 150–158.
28. Baez R, Lopes MTP, Salas CE, Hernandez M. *In vivo* antitumoral activity of stem pineapple (*Ananas comosus*) bromelain. *Planta Med*. 2007; 73: 1377–1383.
29. Belanger-Quintana A, Burlina A, Harding CO, Muntau AC. Up to date knowledge on different treatment strategies for phenylketonuria. *Mol Genet Metab*. 2011; 104: S19–S25.
30. Berg A, Peters M, Deibert P, Koenig D, Birnesser H. Bromelain- Übersicht und Diskussion zur therapeutischen Anwendung und seiner Bedeutung in der Sportmedizin und Sporttraumatologie. *Deutsche Zeitschrift für Sportmedizin*. 2005; 56: 12–19.
31. Borrelli F, Capasso R, Severino B. Inhibitory effects of bromelain, a cysteine protease derived from pineapple stem (*Ananas comosus*), on intestinal motility in mice. *Neurogastroent Motil*. 2011; 23: 745–E331.
32. Brakebusch M, Wintergerst U, Petropoulou T, Notheis G, Husfeld L, Belohradsky BH, et al. Bromelain is an accelerator of phagocytosis, respiratory burst and killing of candida albicans by human granulocytes and monocytes. *Eur J Med Res*. 2001; 6: 193–200.
33. Brien S, Lewith G, Walker A, Hicks SM, Middleton D. Bromelain as a treatment for osteoarthritis: a review of clinical studies. *Evid-Based Compl Alt*. 2004; 1: 251–257.
34. Buttner L, Achilles N, Bohm M, Shah-Hosseini K, Mosges R. Efficacy and tolerability of bromelain in patients with chronic rhinosinusitis—a pilot study. *B-Ent*. 2013; 9: 217–225.
35. Chobotova K, Vernallis AB, Majid FAA. Bromelain's activity and potential as an anti-cancer agent: current evidence and perspectives. *Cancer Lett*. 2010; 290: 148–156.
36. Desser L, Holomanova D, Zavadova E, Pavelka K, Mohr T, Herbacek I. Oral therapy with proteolytic enzymes decreases excessive TGF-beta levels in human blood. *Cancer Chemoth Pharm*. 2001; 47: S10–S15.
37. Dhandayuthapani S, Perez HD, Paroulek A, Chinnakkannu P, Kandalam U, Jaffe M, et al. Bromelain-induced apoptosis in GI-101A breast cancer cells. *J Med Food*. 2012; 15: 344–349.
38. Eckert K, Grabowska E, Stange R, Schneider U, Eschmann K, Maurer HR. Effects of oral bromelain administration on the impaired immunocytotoxicity of mononuclear cells from mammary tumor patients. *Oncol Rep*. 1999; 6: 1191–1199.
39. Enomoto T, Mineshita S, Shigei T. Protective effect of stem bromelain against adrenaline pulmonary edema, and its dependence on the proteolytic activity. *Jpn J Pharmacol*. 1968; 18: 260–265.
40. Fahey T, Stocks N, Thomas T. Systematic review of the treatment of upper respiratory tract infection. *Arch Dis Child*. 1988; 79: 225–230.
41. Fitzhugh DJ, Shan SQ, Dewhirst MW, Hate LP. Bromelain treatment decreases neutrophil migration to sites of inflammation. *Clin Immunol*. 2008; 128: 66–74.
42. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology*. 2007; 20: 1–136.
43. Gaspani L, Limiroli E, Ferrario P, Bianchi M. *In vivo* and *in vitro* effects of bromelain on PGE(2) and SP concentrations in the inflammatory exudate in rats. *Pharmacology*. 2002; 65: 83–86.
44. Gilead L, Mumcuoglu KY, Ingber A. The use of maggot debridement therapy in the treatment of chronic wounds in hospitalised and ambulatory patients. *J Wound Care*. 2012; 21: 78.
45. Harrach T, Eckert K, Schulzeferster K, Nuck R, Grunow D, Maurer HR. Isolation and partial characterization of basic proteinases from stem bromelain. *J Protein Chem*. 1995; 14: 41–52.
46. Harrach T, Gebauer F, Eckert K, Kunze R, Maurer HR. Bromelain Proteinases Modulate the Cd44 Expression on Human Molt-4/8 Leukemia and Sk-Mel-28 Melanoma-Cells *in Vitro*. *Int J Oncol*. 1994; 5: 485–488.
47. Heinicke R, Gortner W. Stem bromelain, a new protease preparation from pineapple plants. *Econ Bot*. 1957; 11: 225–234.
48. Huang JR, Wu CC, Hou RCW, Jeng KC. Bromelain inhibits lipopolysaccharide-induced cytokine production in human THP-1 monocytes via the removal of CD14. *Immunol Invest*. 2008; 37: 263–277.
49. Inchingolo F, Tatullo M, Marrelli M, Inchingolo AM, Picciariello V, Inchingolo AD, et al. Clinical trial with bromelain in third molar exodontia. *Eur Rev Med Pharmaco*. 2010; 14: 771–774.
50. Kalra N, Bhui K, Roy P, Srivastava S, George J, Prasad S, et al. Regulation of p53, nuclear factor KB and cyclooxygenase-2 expression by bromelain through targeting mitogenactivated protein kinase pathway in mouse skin. *Toxicol Appl Pharm*. 2008; 226: 30–37.
51. Kolac C, Streichhan P, Lehr CM. Oral bioavailability of proteolytic enzymes. *Eur J Pharm Biopharm*. 1996; 42: 222–232.
52. Kempf K, Mauzo G. Effect of combined oral proteases and flavonoid treatment in subjects at risk of Type 1 diabetes. 2009; 26: 1309–1310.
53. Leggett JE. Acute sinusitis: when-and when not-to prescribe antibiotics. *Postgrad Med*. 2004; 115: 13–19.
54. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008; 454: 436–444.
55. Menon V, Harrington RA, Hochman JS, Cannon CP, Goodman SD, Wilcox RG, et al. Thrombolysis and adjunctive therapy in acute myocardial infarction. *Chest*. 2004; 126: 549s–575s.
56. Miller JM, Opher AW. Increased proteolytic activity of human blood serum after oral administration of bromelain. *Exp Med Surg*. 1964; 22: 277.
57. Muller S, Marz R, Schmolz M, Drewelow B, Eschmann K, Meiser P. Placebo-controlled randomized clinical trial on the immunomodulating activities of low- and high-dose bromelain after oral administration new evidence on the antiinflammatory mode of action of bromelain. *Phytother Res*. 2013; 27: 199–204.
58. Netti C, Bandi G, Pecile A. Anti-inflammatory action of proteolytic enzymes of animal, vegetable or bacterial origin, administered orally compared with that of known antiphlogistic compounds. *Il Farmaco Ed Pr*. 1996; 27: 453–466.
59. Ogino M, Majima M, Kawamura M, Hatanaka K, Saito M. Increased migration of neutrophils to granulocyte-colony stimulating factor in rat carrageenin-induced pleurisy: roles of complement, bradykinin, and inducible cyclooxygenase-2. *Inflamm Res*. 1996; 45: 335–346.
60. Ohishi S, Uchida Y, Ueno A, Katori M. Bromelain, a thiolprotease from pineapple stem, depletes high molecular-weight kininogen by activation of hageman-factor (factor-XII). *Thromb Res*. 1979; 14: 665–672.
61. Pillai K, Akhter J, Chua TC, Morris DL. Anticancer property of bromelain with therapeutic potential in malignant peritoneal mesothelioma. *Cancer Invest*. 2013; 31: 241–250.
62. Reddy VB, Lerner EA. Plant cysteine proteases that evoke itch activate protease-activated receptors. *Brit J Dermatol*. 2010; 163: 532–535.
63. Secor ER, Carson 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: 68–75.
64. Secor ER, Carson WF, Singh A, Pensa M, Guernsey LA, Schramm CM, et al. Oral bromelain attenuates inflammation in an ovalbumin-induced murine model of asthma. *Evid-Based Compl Alt*. 2008; 5: 61–69.

65. Shigei T, Sakuma A, Nishiwaki T. A study on the protective effect of bromelain, crude pineapple proteases, against adrenaline-induced pulmonary edema in rats. *Jpn Heart J.* 1967; 8: 718–720.
66. Smyth RD, Brennan R, Martin GJ. Systemic biochemical changes following the oral administration of a proteolytic enzyme, bromelain. *Arch Int Pharmacodyn Ther.* 1962; 136: 230–236.
67. Uhlig G, Seifert J. The effect of proteolytic enzymes (traumanase) on posttraumatic edema. *Fortschr Med.* 1981; 99: 554–556.
68. Vellini M, Desideri D, Milanese A, Omini C, Daffonchio L, Hernandez A, et al. Possible involvement of eicosanoids in the pharmacological action of bromelain. *Arzneimittel-Forsch.* 1986; 36: 110–112.
69. Yuan G, Wahlqvist ML, He G, Yang M, Li D. Natural products and antiinflammatory activity. *Asia Pacific J Clinical Nutr.* 2006; 15: 143–152.