Bromelain as an anti-inflammatory and anti-cancer compound

Siavash Hosseinpour Chermahini

The University of Georgia, Kostava St. 77a, 0171 Tbilisi, Georgia

ABSTRACT

Inflammation is a complicated problem for today’s human beings. Large numbers of people have been diagnosed with arthritis along with inflammation. This is beside the others that suffer inflammation caused by an injury. There are alternatives that can be considered as temporary or permanent treatments of chronic inflammatory diseases. Plants, as well as other biological resources, are most welcomed to the therapeutic area. Using the plants’ compounds with high potential as novel techniques are today’s bio-pharmacologist concern. Bromelain has been more attractive due to its characteristics. This review is an overview of anti-inflammatory and anti-cancer effect of bromelain as a confident treatment for all inflammatory disease.

Keywords: Anti-cancer; Anti-inflammatory; Bromelain, Inflammation.

INTRODUCTION

Bromelain is a type of proteolytic enzyme present in the tissues of the plant family Bromeliaceae, of which pineapple is the best known source [1]. Lesser size presented is (EC 3.4.22.32) with 23.8 kDa thiol proteinase Bromelain is a combination of various thiol endo peptidases and other elements like phosphatases, glucosidase, peroxidases, cellulases, glycoproteins, carbohydrates, and several protease inhibitors [2]. The enzymatic activities of bromelain comprise a wide spectrum with pH range of 5.5 to 8.0 [3]. Different protein fractions were obtained by means of various “biochemical techniques as sodium dodecyl sulphate polyacrylamide gel electrophoresis” (SDS-PAGE), isoelectric focusing (IEF), and multicathodal PAGE [4]. Nowadays, bromelain is prepared from cooled pineapple juice by centrifugation, ultrafiltration, and lyophilization. The process yields a yellowish powder, the enzyme activity of which is determined with different substrates such as casein (FIP unit), gelatin (gelatin digestion units), or chromogenic tripeptides [5]. Bromelain derived from stem of pineapple (Ananas comosus L. Merryl) [6], may offer such an alternative for nonsteroidal anti-inflammatory drugs [7]. There is accumulating evidence showing the role of NF-kB signaling and over-expression in many types of cancers [8,9]. Emerging evidences also suggest that depending on the cell context, NF-kB can also promote tumor suppression [10]. Among multiple target genes of NF-kB is Cox-2, a key player in chronic and cancer-related inflammation [11,12]. Bromelain was shown to down-regulate the NF-kB and Cox-2 expression in mouse papillomas [13] and in models of skin tumorigenesis [14]. Additionally, in human monocytic leukemia and murine microglial cell lines, bromelain was shown to inhibit bacterial endotoxin (LPS)-induced NF-jB activity as well as the expression of PGE2 and Cox-2 [15,16].

Absorption and Bioavailability

The body is able to absorb a large amount of bromelain (about 12 gm/day) without facing any major negative effects. Bromelain is absorbed by the gastrointestinal tract without being reduced where 40% of labelled bromelain can be absorbed in complex molecular form [2]. Bromelain was found to hold its proteolytic activity in plasma and was also found to link to the alpha 2-mac-
Table 1: Cellular and molecular targets of bromelain related to its anti-inflammatory activity [17]

| Target | Experimental approach | Effect |
|--------|-----------------------|--------|
| Neutrophils (human, healthy donors) | In vitro Wobenzym treatment | ROS cytotoxicity towards tumor cell lines in vitro |
| Neutrophils (human, healthy donors) | In vitro bromelain | Chemicals towards IL-8 |
| Neutrophils (mice) | In vivo bromelain + thiglycollate | Migration towards inflammatory stimulus |
| CD4(+) T cells, activated (mice) | In vivo bromelain | CD27 |
| Peritoneal lavage fluid (mice) | In vivo bromelain + thiglycollate (inflammatory signal) | KO (IL-6), TNF-α, IL-4, IL-10, IL-6, MIP-1α, MCP-1, IL-12 |
| Macrophages (mouse) | In vivo bromelain treatment + IFN-γ | TNF-α, NO, IL-6 |
| Macrophages (mouse) | In vivo bromelain treatment + LPS | NO, TNF-α |
| NK cells (mouse) | In vivo bromelain treatment = IL-2 + IL-12 | IFN-γ |
| PBMC (human, healthy donors) | In vivo bromelain followed by in vitro assay = IFN-γ | TNF-α, IL-10, IL-6 |
| PBMC (human, healthy donors) | In vivo bromelain + LPS | TNF-α, IL-10, IL-6 |
| PBMC (human, healthy donors) | In vivo bromelain + CD2 | Inhibition of lymphocytes |
| Blood samples from healthy donors (human) | Oral bromelain | AK cell activity monocytic cytotoxicity IL-1β, PTI, PI, plasminogen |
| Blood samples from healthy donors (human) | Oral bromelain (Wob-enzyme) | ROS production in polymorphonuclear neutrophils |
| Blood samples from breast cancer patients | Oral bromelain | G-CSF, GM-CSF, IL-6, TNF-α, CCL4, MIP-1β |
| IBD biopsies (human) | In vivo bromelain | TGF-β |
| Serum of RA, OMIF, RA patients with elevated TGF-β | Phosphorylation | Anti-bromelain antibodies |
| Serum of mice | Oral immunization with bromelain | Anti-bromelain antibodies |
| Tumors (mouse: chemically-induced skin papillomas, injected tumor cell lines: sarcoma L-1, B-16, leukemia, sarcoma (S-37), Ehrlich ascites tumor, Lewis lung carcinoma, mammary adenocarcinoma) | Intraperitoneal immunization with bromelain | Anti-bromelain antibodies |
| Tumor cell lines (mesenchymal melanoma) | In vivo bromelain treatment | Apoptosis, N-ASA, COX-2, growth, metastasis |
| Tumor cell lines (human glioma) | In vivo bromelain treatment | VEGF, viability, LIF |
| Tumor cells (human monocyte leukemia) | In vitro + LPS | NF-κB, VEGF, COX-2, IPGE |
| Hemostatic system (human) | In vivo + thrombin/ TRAP 6-ADP | Activated platelets aggregation, platelet aggregation, Blood coagulation, thrombosis formation |
| Kidney cells (pig) | In vivo bromelain treatment | AGE product induced genotoxicity |

The effects of bromelain are marked as follow: decreased, increased = unchanged.

Bromelain is a proteolytic enzyme that can function as a blood anticoagulant and a fibrinolytic agent. It is also a known protease inhibitor, capable of inhibiting a variety of enzymes including alpha1-antitrypsin, alpha1-antichymotrypsin, and antithrombin III. In clinical studies, bromelain has been demonstrated to have beneficial effects on a variety of conditions, including respiratory disorders, digestive problems, and metabolic disorders. However, it is important to note that the potential for adverse effects and interactions with other medications must be considered.

Medicinal Uses of Bromelain in the Body

Clinical studies have shown that bromelain can help in the treatment of several disorders. Bromelain has a wide range of applications such as being a cleansing agent, meat tenderizer, a digestive aid, and an anti-inflammatory agent. The year of 2001 Maurer was the first who showed characteristics in bromelain as a fibrinolytic agent and an antibiotic potentiating agent, etc. [2]. These enzymes are classified according to their inactivation ability. For instance, in case of Ananain, it will rapidly become inactivate with white proteinase inhibitor cystatin of chicken egg and trans-epoxy-succinyl-l-leucylamido (4-guanidino) butane, but for fruits, it will happen very slowly [4]. It was also shown through in-vitro experiments that bromelain has the ability to control surface adhesion molecules on T cells, macrophages, and natural killer cells and also induce the secretion of IL-1, IL-6, and tumour necro-
sis factor-α (TNF-α) by peripheral blood mononuclear cells (PBMCs) \[19\]. There are also other proven benefits from using bromelain. For example, it was found that oral therapy with bromelain produces certain analgesic and anti-inflammatory effects in patients with rheumatoid arthritis, one of the most common autoimmune diseases \[20\]. In a multi-centre study conducted in Germany, it was reported that bromelain produced a positive outcome compared to placebo for patients with arthritis \[21\]. In a more recent study, a double blinded trial was conducted to compare the oral enzyme preparation of Phlogenzym (containing bromelain, with trypsin and rutin) with an NSAID (diclofenac) during a 3-week treatment among 73 patients suffering osteoarthritis of the knee \[22\]. There is also experimental evidence of its effects on blood coagulation where increases in the serum fibrinolytic activity and prostaglandin levels have been recorded due to a decrease in PGE2 and thromboxane A2. Essentially, this phenomenon is important for reducing inflammation \[1\]. The role of the analgesic is a secondary effect on factors of reducing pain-inducing, contains immune complexes, debris, and oedema \[22\]. Moreover, for cases like bradykinin it has found its direct influence effect on pain mediators. For instance, it was shown when bradykinin was used directly onto surgically denuded blisters, it highly reduced pain response \[23\]. Statistics studies on humans and some animals demonstrated anti-inflammatory effects of bromelain administration orally, showing low levels of absorbance after oral administration. In human, the plasma level is less than 10 mg/ml by treating 4 g/daily \[23, 24\]. This will happen due to bromelain inhibition by alpha-2- macroglobulin that is the plasma protease inhibitor \[25\]. It was also concluded based on existing proofs that bromelain can be a promising candidate for the develop-

| Established mechanisms | Research directions |
|------------------------|---------------------|
| **Inhibition of tumor cell growth and metastasis** | | 
| Stimulation of apoptosis activators and inhibition of cell survival activators in tumor cells | Bromelain effects on cell survival and apoptosis regulators in human cancer cell lines and primary cells |
| Cleavage of CD44 | Bromelain effect on tumor markers of adhesion and invasion |
| **Regulation of inflammatory mediators** | | 
| Inhibition of NF-kB/COX-2/PGE2 expression in tumor cells | Bromelain effect on TNF-α, IL-1β, IL-6 and IFNγ in cancer patients-derived immune cells |
| Regulation of inflammatory cytokines and growth factors (TNF-α, IL-1β, IL-6 and IFNγ) | | 
| Regulation of AGE mediated pathways | Bromelain effect on RAGE expression in cancer cells; Bromelain-RAGE mediated effect on NF-κB |
| **Immuno-modulatory activity** | | 
| CD44-mediated activation of lymphocytes | Bromelain effect on CD44-mediated activation of cancer patient-derived lymphocytes |
| CD25-mediated modulation of T lymphocytes activity | Bromelain effect on CD25-dependent response of cancer patient-derived lymphocytes |
| Stimulation of neutrophils | Bromelain effect on ROS production in cancer patients-derived neutrophils |
| Stimulation of monocytic cytotoxicity Down-regulation of immune system inhibitor (TGFβ) | Bromelain effect on TGFβ and IL-10 expression in cancer cells |
| Induction of antibodies that cross-react with cancer-expressed targets | Analysis of human anti-cancer targets of anti-bromelain antibodies |
| **Alteration of tumor micro-environment** | | 
| Reduction of immune cells infiltration | Bromelain effect on tumor infiltrate in human cancers |
| Changing profile of secreted mediators (chemokines) | Bromelain effect on chemokine and chemokine receptors expression in tumor cells |
| **Regulation of haemostatic system** | | 
| Inhibition of platelets activation and aggregation | Bromelain effect on cancer patients-derived platelet activation and aggregation |
| Reduction of blood coagulation capacity | Bromelain effect on coagulation parameters of cancer patients-derived blood |
| Reduction of elevated levels of soluble fibrin | Fibrinolytic ‘un-coating’ tumor cells and exposing them to immuno-editing |

Table 2: Established mechanisms of anti-inflammatory and anti-cancer activity of bromelain and future research directions \[21\]
ment of future oral enzyme therapies for oncology patients. This is so because bromelain is able to be absorbed in human intestines without degradation and loss of its biological activity \[27\]. There are documents that prove the proteolytical property of bromelain will cause to the removing of some cells that affects the migration of lymphocytes and their activity \[27\]. In the case of humans, there are some significant examples like collagen or adjuvant-induced arthritides \[26\], Ig E-mediated perennial allergic rhinitis \[27\], experimental allergic encephalomyelitis (EAE), autoimmune disease multiple sclerosis \[29\], and also some human rheumatologic diseases \[29\]. These findings demonstrated that the concentration of bromelain systemically delivered to affect cell surface bromelain-sensitive molecules should be more than the time it delivers topically \[2\]. Therefore, in the case of IBD, we conclude that the anti-inflammatory effects of bromelain, orally used, are similar to the local proteolytic activity ofintestinal lumen, then systemic activity. Based on the reports, almost three-quarters of bromelain-administered patients have reported complete or close to full reduction of swelling effect with a reduction in soreness and pain. Meanwhile, small-scale studies have demonstrated anti-inflammatory effects of bromelain for ulcerative colitis \[23\] and also urogenital tract \[30\].

**CONCLUSION**

As mentioned, detailed, the role of bromelain as an anti-inflammatory and anti-cancer agent is thought to be multifaceted. Bromelain has been suggested as an adjuvant therapeutic treatment for diseases which are chronic inflammatory, malignant, and autoimmune.

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