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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.

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Corresponding Author

Name: Dr. Siavash Hosseinpour Chermahini
Email: S.chermahini@ug.edu.ge

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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	↓ Chemotaxis towards IL-8
Neutrophils (mice)	In vivo bromelain + thioglycollate	↓ Migration towards inflammatory stimulus
CD4(+) T cells, activated (mice)	In vitro bromelain	↓ CD25
Peritoneal lavage fluid (mice)	In vivo bromelain + thioglycollate (inflammatory signal)	↑KC(IL-8), =IFNγ, =TNFα, =IL-4, =IL-10, =IL-6, =MIP-1α, =MCP-1, =IL-12
Macrophages (mouse)	In vitro bromelain treatment + IFNγ	↑ TNFa,↑NO
Macrophages (mouse)	In vitro bromelain treatment + LPS	=NO, =TNFa
NK cells (mouse)	In vitro bromelain treatment + IL-2 + IL-12	↑ IFNγ
PBMC (human, healthy donors)	In vitro bromelain	↑TNFα, ↑IL-1β, ↑IL-6,↑IFNγ,↑GM-CSF
PBMC (human, healthy donors)	In vivo bromelain followed by in vitro assay + IFNγ	↑TNFα,↑IL-1β,↑IL-6
PBMC (human, healthy donors)	In vitro bromelain + LPS	↓TNFα, ↓IL-1β, ↓IL-6
PBMC (human, healthy donors)	In vitro bromelain + CD2	↑ Proliferation of lymphocytes
PBMC (human, healthy donors)	In vitro bromelain	↓ CD44 ↓CD128a/CXCR1,↓CD128b/CXCR2,↓CD7, ↓ CD8a, ↓CD14,↓CD16,↓ CD21, ↓CD41, ↓CD42a, ↓D45RA,↓CD48, ↓CD57,↓CD62L
Blood samples from healthy donors (human)	Oral bromelain	↓LAK cells activity =monocytic cytotoxicity,↑ IL-1β, ↑ PTT, =PT, =plasminogen
Blood samples from healthy donors (human)	Oral bromelain (Wobenzym)	↑ROS production in polymorphonuclear neutrophils
Blood samples from breast cancer patients	Oral bromelain	↓CD44 on lymphocytes,↑monocytic cytotoxicity (MAK and bMAK cell activity), =IL-1β, =NK cell activity, =LAK activity
IBD biopsies (human)	In vitro bromelain	↓ G-CSF,↓GM-CSF,↓IFN-γ,↓TNFα,↓CCL4/MIP1β
Serum of RA, OMF, HZ patients with elevated TGFb	Pholygenzyme	↓TGF-b
Serum of mice	Oral immunization with bromelain	↑Anti-bromelain antibodies
Serum of mice	Intraperitoneal immunization with bromelain	↑ Anti-bromelain antibodies
Tumors (mouse; chemically-induced skin papillomas; injected tumor cell lines: sarcoma L-1, P-388 leukemia, sarcoma (S- 37), Ehrlich ascitic tumor, Lewis lung carcinoma, mammary adenocarcinoma)	In vivo topical or intraperitoneal bromelain application	↑Apoptosis,↓NF-kB,↓Cox-2,↓growth,↓metastasis
Tumor cell lines (mouse melanoma)	In vitro bromelain treatment	↓ Viability, ↑growth
Tumor cell lines (human glioma)	In vitro bromelain treatment	↓CD44,↓integrin α3β1,↓adhesion,↓invasion,↓migration, =viability
Tumor cells (human monocytic leukemia)	In vitro + LPS	↓NF-kB,↓Cox-2,↓PGE2
Haemostatic system (human)	In vivo	↓ Platelets aggregation
Haemostatic system (human)	In vitro + thrombin/ TRAP-6/ADP	↓platelets count,↓platelets aggregation,↓ platelets activation,↓Blood coagulation,↑fibrinolysis, ↓ thrombus formation
Kidney cells (pig)	In vitro bromelain treatment	↓ AGE product-induced genotoxicity

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

roglobulin and alpha1-antichymotrypsin, the two antiproteinases of blood. In a recent research, 3.66mg/mL of bromelain was shown to be stable in the artificial stomach juice after 4 hrs of reaction while 2.44 mg/mL of bromelain endured in the artificial blood after 4 hrs of reaction [18].

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-

Table 2: Established mechanisms of anti-inflammatory and anti-cancer activity of bromelain and future research directions [2]

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 Regulation of inflammatory cytokines and growth factors (TNF-α, IL-1β, IL-6 and IFNγ)	Bromelain effect on TNF-α, IL-1β, IL-6 and IFNγ in cancer patients-derived immune cells
Regulation of AGE mediated pathways	Bromelain effect on RAGE expression in cancer cells; Bromelain-RAGE mediated effect on NF-kB
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 (TGFb)	Bromelain effect on TGFb 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

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 proteinase inhibitor [25]. It was also concluded based on existing proofs that bromelain can be a promising candidate for the develop-

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 [17]. 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 [7]. In the case of humans, there are some significant examples like collagen or adjuvant-induced arthritis [26], Ig Emediated perennial allergic rhinitis [27], experimental allergic encephalomyelitis (EAE), autoimmune disease multiple sclerosis [28] 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 of intestinal 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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