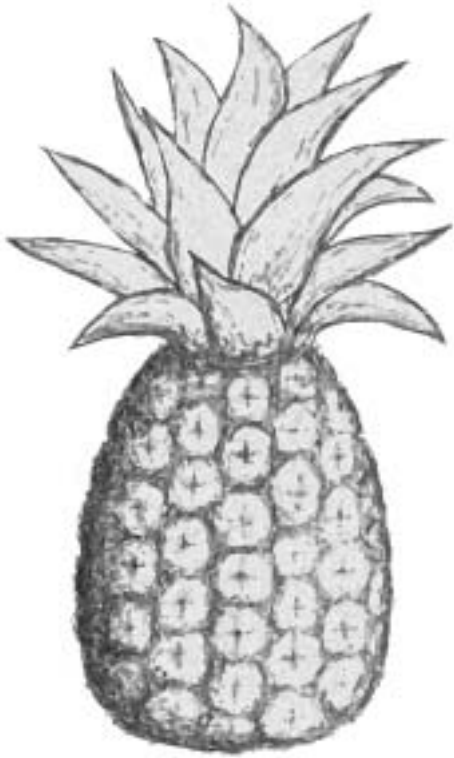


# Monograph



## Bromelain

### Description and Constituents

Bromelain is a general name for a family of sulfhydryl-containing, proteolytic enzymes obtained from *Ananas comosus*, the pineapple plant. Bromelain's primary component is a sulfhydryl proteolytic fraction. Bromelain also contains a peroxidase, acid phosphatase, several protease inhibitors, and organically-bound calcium. It appears a great deal of the physiological activity of bromelain cannot be accounted for by its proteolytic fraction and that the beneficial effects of bromelain are due to multiple factors, not to one single, isolated factor.

A variety of designations have been used to indicate the activity of bromelain, with published research varying in the designation utilized. Rorer units (r.u.), gelatin dissolving units (g.d.u.), and milk clotting units (m.c.u.) are the most commonly used measures of activity. One gram of bromelain standard-

ized to 2000 m.c.u would be approximately equal to 1 gram with 1200 g.d.u. of activity or 8 grams with 100,000 r.u. of activity.

### Pharmacokinetics

Bromelain is absorbed intact through the gastrointestinal tract of animals, with up to 40 percent of the high molecular weight substances detected in the blood after oral administration. The highest concentration of bromelain is found in the blood one hour after administration; however, its proteolytic activity is rapidly deactivated.<sup>1</sup>

### Mechanisms of Action

Bromelain's anti-inflammatory activity appears to be due to a variety of physiological actions. Evidence indicates that bromelain's action is in part a result of inhibiting the generation of bradykinin at the inflammatory site via depletion of the plasma kallikrein system, as well as limiting the formation of fibrin by reduction of clotting cascade intermediates.<sup>2-4</sup> Bromelain has also been shown to stimulate the conversion of plasminogen to plasmin, resulting in increased fibrinolysis.<sup>4</sup>

Bromelain might be capable of selectively modulating the biosynthesis of thromboxanes and prostacyclins, two groups of prostaglandins with opposite actions which ultimately influence activation of cyclic-3,5-adenosine, an important cell-growth modulating compound. It is hypothesized that bromelain therapy leads to a relative increase of the endogenous prostaglandins, PGI<sub>2</sub> and PGE<sub>2</sub> over thromboxane A<sub>2</sub>.<sup>5</sup>

Bromelain has been shown to decrease aggregation of blood platelets.<sup>6</sup> It is an effective fibrinolytic agent *in vitro* and *in vivo*; however, its effect is more evident in purified fibrinogen solutions than in plasma.<sup>7</sup>

### Clinical Indications

*Antitumor:* Several studies, both animal and human, indicate bromelain might have some antimetastatic

ability.<sup>8-10</sup> In doses of over 1000 mg daily, bromelain has been combined with chemotherapeutic agents such as 5-FU and vincristine, resulting in tumor regression.<sup>8, 11</sup>

*Immune Modulation:* Bromelain can induce cytokine production in human peripheral blood mononuclear cells. Treatment leads to the production of tumor necrosis factor-alpha, interleukin-1-beta, and interleukin-6 in a time- and dose-dependent manner.<sup>12,13</sup> Bromelain has also been shown to remove T-cell CD44 molecules from lymphocytes and to affect T-cell activation.<sup>14</sup>

*Debridement of Wounds:* Bromelain applied topically as a cream (35% bromelain in a lipid base) can be beneficial in the elimination of burn debris and in acceleration of healing.<sup>15</sup> A non-proteolytic component of bromelain is responsible for this effect. This component, referred to as escharase, has no hydrolytic enzyme activity against normal protein substrates or various glycosaminoglycan substrates, and its activity varies greatly from preparation to preparation.<sup>16</sup>

*Potentiation of Antibiotics:* Antibiotic potentiation is one of the primary uses of bromelain in several foreign countries. In humans, some undetermined activity of bromelain has been documented to increase blood and urine levels of antibiotics.<sup>17-19</sup>

Combined bromelain and antibiotic therapy has been shown to be more effective than antibiotics alone in a variety of conditions including pneumonia, bronchitis, cutaneous staphylococcus infection, thrombophlebitis, cellulitis, pyelonephritis, perirectal and rectal abscesses,<sup>20</sup> and sinusitis.<sup>21</sup>

*Mucolytic:* In a clinical study of 124 patients hospitalized with chronic bronchitis, pneumonia, bronchopneumonia, bronchiectasis, or pulmonary abscess, those receiving bromelain orally showed a decrease in the volume and purulence of the sputum.<sup>22</sup>

*Digestive Aid:* Bromelain has been used successfully as a digestive enzyme following pancreatectomy, in cases of exocrine pancreas insufficiency, and in other intestinal disorders.<sup>23</sup> The combination of ox bile, pancreatin, and bromelain is effective in lowering stool fat excretion in patients with pancreatic steatorrhea and resulting in a symptomatic improvement in pain, flatulence and stool frequency.<sup>24</sup>

Bromelain has been reported to heal gastric ulcers in experimental animals.<sup>25</sup> In an extensive study of the effect of bromelain on the gastric mucosa, it was found that bromelain increased the uptake of radioactive sulfur by 50 percent and glucosamine by 30-90 percent. Increased uptake of these substances may allow the gastric mucosa to heal more rapidly.<sup>26</sup>

*Surgical Procedures and Musculoskeletal Injuries:* Bromelain's most common application is in the treatment of inflammation and soft tissue injuries. It has been shown to speed healing from bruises and hematomas.<sup>27</sup> Treatment with bromelain following blunt injuries to the musculoskeletal system results in a clear reduction in swelling, pain at rest and during movement, and tenderness.<sup>28</sup> Administration of bromelain pre-surgically can reduce the average number of days for complete disappearance of pain and inflammation.<sup>29, 30</sup>

*Cardiovascular and Circulatory Applications:* Research has indicated that bromelain prevents or minimizes the severity of angina pectoris.<sup>31, 32</sup> A drastic reduction in the incidence of coronary infarct after administration of potassium and magnesium orotate along with 120-400 mg of bromelain per day has been reported.<sup>33</sup> In a study involving 73 patients with acute thrombophlebitis, bromelain, in addition to

analgesics, was shown to decrease all symptoms of inflammation; including, pain, edema, tenderness, skin temperature, and disability.<sup>34</sup>

## Toxicity, Side Effects and Allergic Reactions

Bromelain is considered to have very low toxicity, with an LD<sub>50</sub> greater than 10g/kg. Toxicity tests on dogs, with increasing levels of bromelain up to 750 mg/kg administered daily, showed no toxic effects after six months. Dosages of 1.5 g/kg/day administered to rats showed no carcinogenic or teratogenic effects.<sup>35</sup>

In human clinical tests, side effects are generally not observed; however, caution is advised if administering bromelain to individuals with hypertension, since one report indicated individuals with pre-existing hypertension might experience tachycardia following high doses of bromelain.<sup>36</sup>

The allergenic potential of proteolytic enzymes should not be underestimated. They can cause IgE-mediated respiratory allergies of both the immediate type and the late-phase of immediate type.<sup>37</sup> Bromelain, due to its use as a meat tenderizer and to clarify beer, is considered a potential ingestive allergen.

## Dosage

Bromelain has shown therapeutic benefits in doses as small as 160 mg/day; however, it is thought that, for most conditions, best results occur at doses of 750-1000 mg/day. Most research on bromelain has been done utilizing four divided daily doses. Findings indicate that results are dose-dependent.

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