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ETHNOBOTANICAL AND PHARMACOLOGICAL PROPERTIES OF PINEAPPLE PROTEASE (BROMELAIN): A REVIEW

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ABSTRACT

Bromelain (EC 3.4.22.32) is a crude extract from the fruit or stem of pineapple (*Ananas cosmosus* Linn.) plant that contains, among other components various closely related proteinases (stem bromelain, fruit bromelain, comosain and ananain) demonstrating both *in-vitro* and *in-vivo* several therapeutic properties including anti-inflammatory, fibrinolytic, inhibition of platelet aggregation, anticancer, mucolytic, skin debridment, digestive assistance, enhanced wound healing, cardiovascular and circulatory improvement, enhaced absorption of other drugs etc. Bromelain also contains peroxidase, acid phosphatase, several protease inhibitors and remain stable over a wide range of pH 2 to 9. It has earned universal acceptability as a phytotherapeutic drug because of its history of safe use and zero side effects. This review deals with the biochemistry, pharmacology and medicinal use of bromelain.

KEYWORDS: Bromelain, *Ananus cosmosus*, proteinases, Phytotherapeutic.

INTRODUCTION

Pineapple (*Ananas cosmosus* Linn.) native to Central and South America, is grown in several tropical and subtropical countries including India, China, Kenya, South Africa, Malaysia.[1] It has been used as a medicinal plant in several native cultures and bromelain has been chemically known since 1876.[2] It is present in all parts of the plants but stem is the most common source for the commercial preparation of

bromelaine.[3] It was first introduced as therapeutic supplement in 1957, it is currently 13th most widely used herbal medicine in Germany. Although bromelain's primary constituent is a sulfhydryl proteolytic fraction, it also contains escharase (a non proteolytic components in bromelain thought to be important in the action of topical bromelain), peroxidase, acid phosphatase, protease inhibitor and organically bound calcium.[4] It is a mixture of sulphur containing protein digesting enzymes. The popularity of pineapple is due to its sweet-sour taste containing 15% sugar, malic acid and citric fruit acids. It also contains vitamin B1, B2, B6 and C.[5] Flavonoids mainly present as colouring pigments in plants also function as potent antioxidants at various levels they could protect membrane lipids from oxidation.[6,7] When taken orally, bromelain is an effective anti-inflammatory and used to treat a number of inflammatory conditions[8] including bronchitis, sinusitis[9], joint swelling and pain as well as increased joint mobility.[10] It improve effectiveness of antibiotics by increasing their level in blood tissue[11], it also reduce recovery time after surgery.[12]

Several studies have been carried out and results generated indicate bromelain has useful phytomedical applications. The purpose of the present review article is to highlight some relevant contributions regarding bromelains phytomedical applications that have been reported in recent times.

Biochemistry of Bromelain

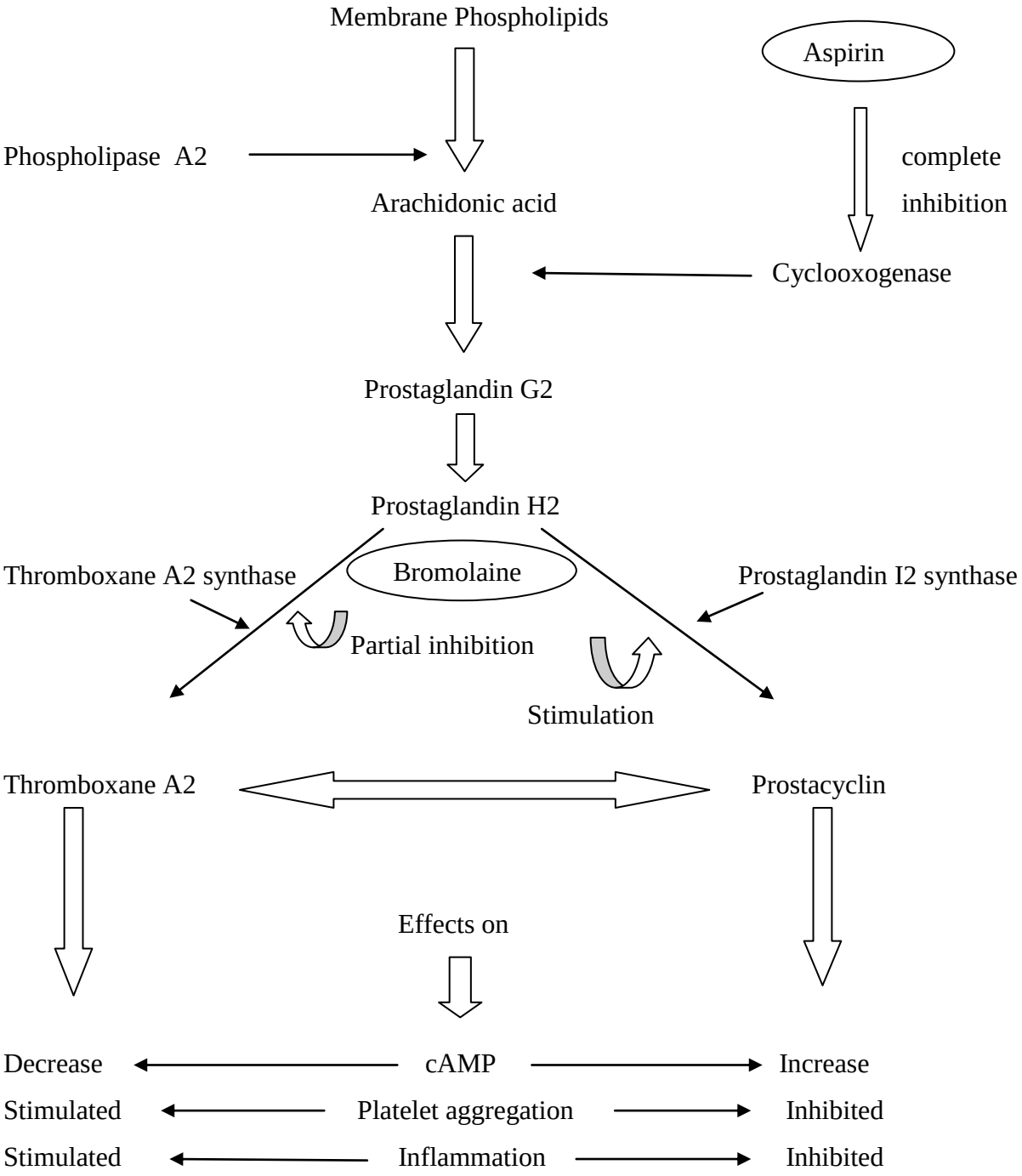
Table 1. Cysteine proteinases from pineapple[17]

Name	Molecular Mass (Dalton)	Isoelectric point	Sequences	Glycosylation
Stem bromelain (EC 3.4.22.32)	23,800 (sequence + sugar)	>10	Completely sequenced (212 amino acid)	Glycosylated
Ananain (EC 3.4.22.31)	23,464 (sequence)	>10	Completely sequenced (216 amino acid)	Not glycosylated
Comosain	23,569	>10	N-term sequence	Glycosylated
Fruit bromelain (EC 3.4.22.33)	23,000	4,6	N-term sequence	Not glycosylated

It is a crude, aqueous extract obtained from the stems and immature fruits of the pineapple (*Ananus cosmosus* Merr. Mainly var. Cayenne from the family bromeliaceae) contain complex mixture of different thiol-endopeptidases and other not yet completely characterized components such as phophatases, glucosidases, peroxidases, cellulases, glycoproteins and carbohydrates.[13] In addition, bromelain contains several proteinase inhibitors.[14,15] Stem bromelain (EC 3.4.22.32) is distinguished from fruit bromelain (EC

3.4.22.33). Today bromelain is prepared from cooled pineapple juice by centrifugation, ultracentrifugation and lyophilization. The process yields yellowish powder whose enzyme activity is determined with various substrates such as casein, gelatin or chromogenic peptides.[16] The enzymatic activities comprise a wide spectrum with pH 5.5 to 8.0. Bromelain prefentially cleaves glycyl, alanyl and leucyl bonds.

Pharmacological Activities of Bromelain



Anti-inflammatory and Analgesic activity: it is result from blocking bradykinin and its modulation of prostaglandin synthesis. It achieves an anticoagulant effect through both reduced platelet aggregation, by increasing relative concentration of prostacyclin and prostaglandin E2 over the concentration of thromboxane A2 and fibrinolysis by activation of plasmin. Plasmin further suppresses inflammation by blocking the mobilization of endogenous araachidonic acid by phospholipases.[18-22]

Anti-cancer activity

Several animal and human studies indicate that bromelain might have some anticancer activity.[23-27] It is result from bromelain ability to affect T-cell activation, induce cytokinin production in circulating monocytes and enhances production of tumor necrosis factor and interleukins. As an adjunct in cancer therapy bromelain may act as immunomodulator by raising the impaired immunotoxicity of monocytes against tumor cells and by inducing the production of T-cells.[28] Bromelain also inhibits the proliferation of different tumor cells in vitro. The inhibitory activity can be traced neither to the proteolytic nor to the or to the platelet aggregation- inhibitory activity.[29]

Anticoagulant and Fibrinolytic activity: The conclusive evidence that bromelain prevents aggreagation of blood platelets was reported.[30] Bromelain also inhibits platelet aggregation in a dose dependent manner in *in- vitro* study.[31] Bromelain also prevents thrombin induced human platelet aggregation and platelet adhesion to bovine endothelial cells. Furthermore, oral and intravenous application reduced thrombus formation in rat mesenteric vessels.[32, 33]

The effectivity of bromelain as effective fibrinolytic agent was tested both *in-vitro* and *in-vivo* conditions. But its efficacy is more evident in purified fibrinogen solution than in plasma. It may be due to presence of antiproteinases in plasma. A dose dependent reduction of serum fibrinogen level is seen in rats following administration of bromelain. The fibrinolytic activity of bromelain has been attributed to enhanced conversion of plasminogen to plasmin, which limits the spread of coagulation processed by degrading fibrin.[34, 35] There is some evidence that bromelain may be able to dissolve coronary thromboses and may be used in treatment of cardiovascular disorders.[36-39]

Anti-helminthes activity: Infections with gastrointestinal nematodes have severe consequences. Plant cysteine proteinases from pineapple have high proteolytic activities that are known to digest nematode cuticle, have low toxicity and have been used in traditional medicines against gastrointestinal nematodes for decades.[40-42]

Wound healing activity: Bromelain contains more than 50 different components and is widely used as an over the counter food additives and is also used in debridement of burn eschar.[42, 43] To exert debrideration action the concentration of enzyme must be 30-100 times higher than the pharmacological dose required for wound healing. They also show collagenolytic activity which is again promotes wound healing activity[44]. Topical bromelain (35% in lipid base) has achieved complete debridement on experimental burns in rat in about 2 days, as compared with collagenase, which required about 10 days, with no side effects or damage to adjacent burned tissue.[45-49]

Effect of bromelain on Immunisystem: It has been used as adjuvant therapeutics in treatment of chronic inflammatory, malignant and autoimmune disorders.[50] In vitro study suggest that bromelain modulate surface adhesion molecules on T-cells, macrophages and NK cells and induce the secretion of IL-1β, IL-6 and TNFα by peripheral blood mononuclear cells.[51,52] Cells with treatment of bromelain decreases the activation of CD4 (+) T cells and reduces the expression of CD25.[53] However oral therapy with bromelain produces analgesic and anti-inflammatory effects in rheumatoid arthritis patient one of the most common autoimmune diseases.[54, 55]

Antibiotic Potentiation and Antimicrobial activity: Bromelain increases blood and urine level of some antibiotics in humans.[56, 57] Using bromelain with antibiotics was shown to be more effective than antibiotics alone in pneumonia, bronchitis, thrombophlebitis, pyelonephritis and rectal abscesses,[58] sinusitis,[59] and UTI.[60] It also shows benefit in pediatric patients with sepsis.[61]

Bromelain also shows antimicrobial activity, incubation of cells with bromelain stimulate phagocytosis and respiratory burst killing of *Candida albicans.*[62] It also very effective in infectetious skin disorders.[63]

Toxicity, Side effects and allergic reaction: Bromelain have very low loxicity, with a LD_{50} more than 10g/kg. It also not showed any serious side effects in human clinical

trials. Anti-bromelain antibody titers have been detected in blood on long term oral therapy in mice.[64] Furthermore, bromelain accepted as safe phytopharmaceuticals.

CONCLUSION

Bromelain has been used for a variety of clinical applications for so many years. Although its mechanism of action has not been completely understood. It may also enhance the absorption of some other agents which is useful when these nutrients are given. Bromelain has been well absorbed on oral administration and shown to be safe at high doses for prolonged periods of time. For the conditions discussed in this review, bromelain has shown itself to be an effective supplement.

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