

Bromelain: an Overview of Applications in Medicine and Dentistry

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Abstract: Bromelain is an enzyme contained in the pineapple fruit, used previously for its anti-inflammatory, anti-fibrinolytic, anti-edema activities. It also has an antibacterial and anti-metastatic action, and it is successfully used in the medical field. There are few research works on its administration on dentistry. However, it has been shown to be very effective in reducing swelling and post-operative edema in oral surgery, and it is also proposed for the treatment of caries and periodontal disease, with the aim to reduce collateral events of pharmacological therapy. We want to underline how its mechanism of action can make this molecule very important in the dental field.

Keywords: Bromelain; bromelain in oral medicine; bromelain in dentistry.

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1. Introduction

Bromelain is a proteolytic enzyme present in the plant of pineapple (*Ananas comosus*). It has been used for a long time in traditional medicine in South-east Asia, Kenya, India, and China because of its anti-inflammatory, anti-fibrinolytic, anti-thrombotic, and anti-edema properties [1]. Bromelain is present in the fruit and stem. It contains different endopeptidases, thiols, and other components such as phosphatase, glucosidase, peroxidase, glycoproteins, and protease inhibitors [2]. Currently, 8 active components of bromelain have been isolated, including the main components called F4 and F5, F9 represents 2% of total proteins and is the most active fraction [3]. Bromelain acts at a pH of 4.5-9.5 [4]. It is absorbed into the human intestine and remains biologically active with about 6-9 h half-life, reaching a peak 1 h after administration [5]. Various names have been used to indicate bromelain activity such as Rorer's unit (r.u.), gelatin dissolution unit (g.d.u.), and milk coagulation units (m.c.u.). These are the most common measures of activity used. One gram of bromelain standardized at 2000 m.c.u. would be approximately equal to 1 gram with 1200 g.d.u. and 8 grams would correspond to 100,000 r.u. of activity [6].

2. Bromelain activity

Bromelain has been shown to be effective both in several *in vivo* and *in vitro* studies. Its anti aggregating action has been demonstrated in patients with previous ischemic problems by decreasing the level of platelet aggregation in the blood in 17 out of 20 subjects examined and normalizing the values in 8 out of 9 subjects who previously had a high platelet

aggregation value after 2h after taking bromelain [7]. Previous in vitro studies have shown that bromelain led to a reduction in platelet aggregation and its activation by proteolytic activity [8,9], especially that of the F9 fraction. Its antiaggregant action also counteracts the formation of platelet agglomerates that can facilitate the metastasis of tumors because the platelet formation is stimulated by tumor cells allowing aggregations that make the action of the immune system difficult, so we can conclude that it has an anti-metastatic action [10-12]. Bromelain has also demonstrated anti-inflammatory action by inhibiting COX-2 expression and PGE2 production in murine microglial cells and human monocytic leukemia cell lines [13].

In addition, it modulates the expression of NF- κ B responsible for the progression of the inflammatory state also in oncological subjects that, through COX 2 and PGE2 leads at the production of angiogenic factors [2,14]. In vitro bromelain has demonstrated the ability to modulate molecular surface adhesion on T cells, macrophages, and natural killer cells and also induces the secretion of IL-1 β , IL-6, and TNF α by the cells themselves [15,16].

In addition, it appears to act by modulating the action of T lymphocytes by interfering in the transduction of the Raf-1 signal, which leads to the reduction of CD4⁺ Th cells by the inhibition of the CD25 expression (receptor for IL-2) [17,18]. Another recognized action of bromelain is its fibrinolytic capacity, which allows reducing plasma levels of fibrinogen and bradykinin, resulting in less edema and inflammation, thus allowing greater reabsorption of fluids at the interstitial level [19].

Bromelain also has an intrinsic antimicrobial activity tested against *Escherichia coli* and *Vibrio cholerae* by acting by modifying the receptor attack sites and influencing the intestinal secretion signaling pathways [20,21]. It seems that it was useful to promote the absorption of other drugs, including some antibiotics such as penicillin and tetracyclines [22]. Bromelain in combination with antibiotic administration has been shown to be more effective than antibiotics alone in the treatment of pneumonia, bronchitis, staphylococcal skin infections, thrombophlebitis, cellulitis, pyelonephritis and in perirectal and rectal abscesses, sinusitis and urinary tract infections. A combination of bromelain, trypsin, and rutin was administered as adjuvant therapy in combination with antibiotics for children with sepsis [23-26]. However, there are currently no studies performed on dental infections.

3. Bromelain in the medical field

Other studies have reported that bromelain prevented the formation of edema and reduced those already existing in a number of animal experiments [27]. As regards toxicity, bromelain has a very low level of toxicity which would make it less harmful than other anti-inflammatory drugs such as cortisone and NSAIDs: according to one study [28], bromelain has a very low toxicity with an LD50 (lethal dose) greater than 10 g/kg in mice, badgers, and rabbits. In dogs, the dose was increased to 750mg/kg without showing toxic effects over time. In a human study, bromelain was administered with a dosage of 3000 FIP units/day over a period of 10 days, and no side effects were found [29]. It was also used in the treatment of patients with osteoarthritis in two formulations: one 90mg and one 45mg and in both cases there was a reduction in inflammation and pain compared to standard treatments, but it remained well tolerated and without the presence of common side effects in other anti-inflammatory drugs [19]. However, the data are conflicting, as, at high doses, bromelain could give gastrointestinal problems [30] and allergic reactions [31,32].

4. Bromelain in dentistry

In dentistry, bromelain has been used for its anti-inflammatory action, especially after extraction of third molars in comparison or in association with other anti-inflammatory drugs. A study performed compared bromelain (100mg for 4-7 days) with placebo, administered in the same way. Although there is no great statistical difference, the bromelain group showed a decrease in inflammation and pain compared to the placebo group [33]. In the study of Odresi et al., bromelain (50 mg every 12h for 7 days) was compared with paracetamol in patients who performed third molar surgery. In the group who took bromelain, less inflammation was seen compared to the group who took paracetamol [34]. In a study carried out by Majid and colleagues, a comparison was made between bromelain and diclofenac where it was seen that the administration of 250mg of bromelain 6h before surgery and for the following 4 days has an analgesic and anti-inflammatory action comparable to that of diclofenac (25mg) after moral third molar surgery [35]. The study carried out by Ghensi et al. comparing dexamethasone 4mg with 40mg of bromelain (taken every 6h starting immediately after the surgical therapy), showed that bromelain is effective in reducing edema but is lower than dexamethasone. However, the anti-edema and anti-inflammatory effects increased by combining dexamethasone and bromelain[36]. In another study, bromelain (40mg every 6h for 6 days) was compared with ketoprofen (100mg), and there was no significant difference [37]. From this, it can be inferred that they have an efficacy comparable to common anti-inflammatory drugs while presenting lower toxicity. A recent literature review has shown that bromelain is effective in reducing inflammation and edema. However, some limitations remain, such as a consensus on bromelain dosages [38]. It was successfully proposed against teeth caries [39] and also against periodontal pathogen for its antibacterial activity [40]. A meta-analysis in 2019 confirms its beneficial action in the extraction of third molars [41].

5. Conclusion

The previous interesting review had analyzed the anti-cancer effects of natural products [42]. Bromelain has anti-inflammatory, anti-tumor, anti-metastatic, antibacterial, anti-edema activity, in the face of almost zero side effects. The use of bromelain-based supplements could be increased in dentistry, and more studies should be performed to establish adequate dosages and protocols.

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Conflicts of Interest

The authors declare no conflict of interest.

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