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Therapeutic uses of pineapple-extracted bromelain in surgical care - A review.

Zehra Abdul Muhammad
Aga Khan University, zehra.abdul@aku.edu

Tashfeen Ahmad
Aga Khan University, tashfeen.ahmad@aku.edu

REVIEW ARTICLE

Therapeutic uses of pineapple-extracted bromelain in surgical care — A review

Zehra Abdul Muhammad, Tashfeen Ahmad

Abstract

Bromelain is an extract obtained from the pineapple plant and is used as a traditional folk remedy for several ailments. In this review, a comprehensive electronic database search was carried out to compile available literature on therapeutic implications of bromelain.

Pharmaceutical value of bromelain has been demonstrated in different surgical sub-specialties. Diverse biological processes like anti-inflammatory, anti-oedematous, analgesic, anti-thrombotic, exfoliation etc. are involved in bromelain's therapeutic actions, mediated through the kallikrein-kinin and arachidonic acid pathways as well as through effects on cell mediated immunity.

Bromelain equals non-steroidal anti-inflammatory drugs as an anti-inflammatory agent, but has been shown to have fewer side effects. In Europe it is approved for oral and topical use, mainly for surgical wounds, inflammation due to trauma and surgery, and debridement of deep burns. Literature suggests a promising role of bromelain in surgical care. More clinical trials to establish its utility as an anti-inflammatory agent in surgical care are recommended.

Keywords: Bromelain, Pineapple, Wound healing, Inflammation, Anti-inflammatory, debridement.

Introduction

Bromelain is a crude extract derived from pineapple plant (Ananas comosus) and contains mixture of proteolytic enzymes and non-enzymatic substances. It is used as a folk remedy by many native cultures like Philippines, Hawaii etc. Several research studies have shown beneficial effects of bromelain in diverse health-related conditions. Bromelain's relevance is evident from reports of its beneficial effects in resolving swelling, inflammation, bruising and pain associated with trauma and surgery. Bromelain is not only effective but also has fewer adverse effects as compared to non-steroidal anti-inflammatory drugs (NSAIDs).[1-6]

In this review, we present the current available scientific literature covering mechanism of action and therapeutic role of bromelain in surgical care and related conditions. Bibliographic search with emphasis on key words 'bromelain, surgery, inflammation, wound' and phrases 'bromelain in surgical care and surgical wound, anti-inflammatory effect of bromelain etc. was carried out from available data using PubMed database filter (year 1957-2016), Google Scholar, Ovid and specific journals were also searched individually. Total 2,880 articles were searched in which 1,550 were with anti-inflammatory effect of bromelain in surgical care. Out of these articles, only most pertinent research articles with oral administered bromelain (separately or in proteolytic enzyme complex) or topical application of bromelain in different surgical care practices were selected. Those articles with intravenous route of bromelain administration as well as those involving bromelain effects on cancer and combination therapies were excluded. Our aim was to review and explore current evidence based primary data with respect to application of bromelain therapy in surgical practice.

Sources

Bromelain has two main sources: Fruit bromelain (EC 3.4.22.33) extracted from pineapple fruit and Stem bromelain (EC 3.4.22.32) extracted from inedible pineapple stem.[7] Stem bromelain is economical to produce; hence it is the more commonly available commercial product. It is composed of endopeptidases (ananain, comosain), phosphatases, glucosidases, peroxidases, escharase, cellulases, glycoproteins, proteinase inhibitors (cystatin), calcium and carbohydrate.[8-11] The proteolytic activity of bromelain is sensitive to storage conditions and biochemical processing thus, it is not practical to take therapeutic amount of bromelain by oral consumption of raw pineapple fruit as a substitute for bromelain supplements.[12]

Mechanism of action

Several in vivo and in vitro studies have been conducted on the anti-inflammatory activity of bromelain but the actual mechanism of anti-inflammatory effect is not fully established.

(a) Kallikrein-kinin pathway

Studies show that bromelain's anti-inflammatory and

Section of Orthopaedics, Department of Surgery, Aga Khan University, Karachi, Pakistan.

Correspondence: Zehra Abdul Muhammad. Email: zehra.abdul@aku.edu

analgesic activity is due to lowering plasmakinin (bradykinin) at inflammatory site and lowering prostaglandin E2 levels. In vitro experiments showed that bromelain activates plasma prekallikrein by activation of factor XII.[13] In rat experiments, it is shown that bromelain-derived plasminogen activator leads to production of plasmin. The plasmin cleaves Hageman factor in a way that results in a strong release of kallikrein but a weak release of thrombin. Intravenous bromelain administration in rats markedly reduced plasma prekallikrein and high molecular weight kininogen 15 minutes after the injection, and the effect lasted for 72 hours.[14]

Bromelain has been demonstrated to inhibit thrombus formation when administered orally and intravenously.[15,16] The effect may be related to reduction in levels of high molecular weight kininogen and weak release of thrombin.

(b) Arachidonic acid pathway

It is also demonstrated that bromelain increases platelet cyclic adenosine monophosphate (cAMP) levels thus increasing prostaglandin (PG) I2 and PGE1 levels. A possible mechanism is suggested that the dominant endogenous prostaglandins being produced must be from the group that increases platelet cAMP levels (prostacyclin, PGE1, etc.). In in-vivo experimentally-induced inflammatory reaction in rats, bromelain was tested for its action on eicosanoids production. It was identified that arachidonic acid cascade was affected by bromelain.[17] Bromelain, when administered orally in doses of 10 and 20 mg/kg, significantly decreased PGE2 and substance P concentrations in the exudate in rats with subcutaneous carrageenan-induced inflammation. In in-vitro experiment, PGE 2 levels were not affected by bromelain although substance P level was increased.[18]

(c) Cell Mediated Immunity

In in-vitro and in-vivo studies, it was observed that bromelain has anti-inflammatory effect by modulating leukocyte cell surface molecules like CD 14, CD 44, CD 16, CD 21, CD 128 a and b which are involved in leukocyte homing, cellular adhesion, induction of pro-inflammatory mediators and immunomodulatory effect on T cells by inhibition of T cell signal transduction, producing effect on Th1, Th2 and immunosuppressive cytokines, etc. Bromelai also reduce P-selectin mediated neutrophil recruitment.[19-21]

Therapeutic uses of bromelain in trauma and surgical care

Several clinical studies have demonstrated beneficial effects of bromelain (Table) in a variety of conditions related to surgical practice, as described below:

Perioperative

1. Orthopaedics: In a clinical trial, patients with long bone fractures were treated with oral bromelain as a proteolytic enzyme combination containing 90 mg bromelain per tablet after surgery. Significant reduction in pain and swelling with accelerated healing was observed as compared to group of patients who were treated with standard anti-inflammatory analgesics.[22]

2. Obstetrics: Bromelain, administered orally, has been shown to be effective in reducing pain, ecchymosis and edema due to episiotomy in a placebo-controlled, double blind study.[23] Another study showed a trend of similar reduction but the difference did not achieve statistical significance.[24]

3. Otolaryngology: In a randomized, placebo-controlled study, it has been reported that oral bromelain minimizes ecchymosis and edema after rhinoplasty.[25]

4. Dentistry: In patients who had undergone surgery for impacted third molar, a randomized controlled study showed that treatment with oral bromelain reduces post-operative erythema, pain and inflammation.[26] Other randomized, double-blind, placebo-controlled clinical trial showed significant reduction in pain by bromelain

Table: Reported therapeutic benefits of bromelain.

Setting	Condition/patients	Outcome	References
Trauma	Blunt soft tissue injury	Reduced swelling and pain, early return to function	30
	Artificially induced hematoma	Rapid hematoma resorption	31,32,33
Orthopaedics	Long bone fractures	Reduced fracture pain and swelling, accelerated fracture healing	21
Sports medicine	Ligament sprains	Reduced pain, swelling and ecchymosis, earlier return to function	34,35,36,37,38
Obstetrics	Episiotomy	Reduced episiotomy pain, ecchymosis and edema	22,23,24
Otolaryngology	Post-rhinoplasty	Reduced ecchymosis and edema	25
Dentistry	Post-extraction of impacted teeth	Reduced erythema, pain and inflammation	26,27,28
Ophthalmology	Cataract surgery	Reduced inflammation and pain	29
Plastic surgery	Open wounds and burns	Effective debridement permitting early skin grafting	39,40,41,42,43,44
Haematology	Cardiovascular and cerebrovascular disease	Reduced platelet aggregation	14,45,46,47

compared to placebo and diclofenac, while yet another trial showed non-significant reduction in inflammation.[27,28]

5. Ophthalmology: In a double-blind, placebo-controlled clinical trial on patients undergoing cataract surgery, it was demonstrated that oral bromelain administered two days prior to surgery and five days post-operatively resulted in significant reduction in inflammation and pain as compared to the placebo group.[29]

Blunt trauma

In a series of patients suffering from blunt trauma injuries to the musculoskeletal system, treatment with bromelain resulted in subjective improvement in swelling, pain, and tenderness at the site of injury with good tolerability, although there was no control group.[30]

In a placebo controlled clinical trial, when subjects with artificially induced haematoma were treated with bromelain, there was a more rapid resorption of the haematoma and a significantly lower volume of haematoma as compared to placebo group.[31] The mechanism of resolution was not reported but in separate animal studies, inhibition of bradykinin generation at injury site and increase in serum fibrinolytic activity were observed, suggesting the probable mechanism of haematoma resolution.[32,33]

Sports injuries

Literature shows mixed results for bromelain use in treatment of sprains and strains. According to some research studies it appears to reduce swelling, bruising, redness and tenderness, and promotes rapid recovery and healing. A double-blind placebo-controlled study was conducted on patients having sports related ankle injuries. Patients treated with oral bromelain had faster recovery as compared to placebo group.[34] In three small double-blind studies, oral bromelain significantly healed bruises and improved mild athletic injuries as compared to placebo group.[35-37]

Contrary to this, in one big double-blind, placebo-controlled randomized trials, patients with acute unilateral sprain of the lateral ankle joint were treated either separately or in combination with oral bromelain, trypsin or a bioflavonoid rutin. Results showed significant difference in pain, swelling and range of motion as compared to placebo treated group.[38]

Skin wounds

Topical application of bromelain to skin wounds and burns has been shown to be a safe and effective method for debridement of necrotic tissue and is an alternate to surgical debridement.[39,40] Local application of bromelain has been shown to be rapid, effective, non-invasive, safe, easily performed at the bedside with minimal or no blood loss and negligibly interfere with natural wound healing processes.[41]

Debridement of necrotic tissue is due to a non-proteolytic component Escharase having molecular weight of 45,000 Daltons and is present in bromelain extract which also helps in healing. Houck described method of isolating escharase from stem of pineapple plant. Escharase helps in digestion, dissection and separation of non-viable, devitalized tissue, especially eschar tissue between the viable native and the non-viable denatured burn tissue.[42]

A multi-center, open-label, randomized, controlled clinical trial was conducted on patients 4 to 55 years of age with deep partial and full thickness burns. Patients were treated with a bromelain-rich topical agent NexoBrid which was applied for 4 hours or by standard of care. There was reduced time from to complete debridement, need for surgery and need for autografting in bromelain treatment group.[43]

Coagulation

It has been reported that oral administration of bromelain significantly lowers adenosine phosphate induced platelet aggregation. Antiplatelet activity was determined ex vivo.[44] In one study, effect of bromelain was assessed on human plasma fibrin (ogen) and blood coagulation. Bromelain showed dual action on blood coagulation: at low concentration showed procoagulant effect and at high concentration anticoagulant effect.[45] These findings are of concern for surgeons and care needs to be exercised in patients with bleeding disorders while prescribing bromelain.

Contrary to above mentioned findings, some authors identified that bromelain does not significantly affect blood clotting mechanism in healthy volunteers. In one clinical trial, healthy volunteers and breast cancer patients were treated with oral bromelain. The activated partial thromboplastin time increased from 38 to 46 seconds, leaving prothrombin time and plasminogen unchanged.[46] In another clinical trial, patients with oedema and inflammation were treated with 40 mg oral bromelain 4 times daily for 1 week. There was no significant effect on bleeding, coagulation and prothrombin time suggesting that therapeutic amount of bromelain does not affect blood clotting.[47]

Approvals

On the basis of available positive research evidence, the German Commission E approved bromelain as an effective remedy to treat inflammation after ear, nose, throat and trauma surgeries.[48] In the United States, bromelain is "generally recognized as safe" (21CFR184.1024) by the U.S. Food and Drug Administration (FDA), though no approved therapeutic indications are available due to lack of required body of research evidence.

Side effects

Although bromelain is generally safe, there are rare reports of nausea, vomiting, diarrhea, allergic reaction and unusual menstrual bleeding.[49,50] As safety data is scarce, it is advisable that pregnant women, patients with bleeding disorders, hypertension, liver disease and kidney disease should avoid bromelain.[51,52]

Bromelain's role against platelet aggregation may increase the risk of bleeding during and after surgery. It should be administered in patients under doctor's supervision with special precautions. It is recommended that bromelain should not be combined with anticoagulant drugs such as warfarin, clopidogrel etc. and should not be administered in bleeding disorders.

Dosage

Therapeutic management with bromelain is based on medical condition for which it is being taken.

Adults

◆ The German Commission E recommended dosing in ENT surgeries and trauma to be 80 - 320 mg orally 2 - 3 times per day for 8 days. For certain conditions higher doses are also prescribed.

◆ For debridement of deep thermal skin burns, bromelain is applied topically once for 4 hours in the form of debrase gel dressing. Treatment is provided in specialized burn centers under strict observation. Bromelain gel should not be applied to more than 15% of the patient's total body surface area and to the broken skin.

Paediatric

Bromelain is not recommended in children as there is no reliable safety data available. A Paediatric Investigation Plan (EMEA-000142-PIP02-09-M03) has been agreed by European Medicines Agency (Decision number P/0072/2014) and its proposed date of completion is March 2019.[48]

Conclusion

Literature search of 59 years suggest a promising role of bromelain in surgical care on account of its anti-inflammatory effect. Pineapple extracted Bromelain may be used as a therapeutic agent in surgical care.

In surgical practice, further exploration of bromelain's role as a therapeutic anti-inflammatory agent remains to be established through more number of randomized controlled clinical trials.

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