Ananas

Ananas sativus Schult. f.

Nome botanico

Ananas sativus Schult. f.

sinonimo: *Ananas comosus* L. Merr. (*Bromeliaceae*)

Parti usate

Gambo del frutto.

Componenti principali

Bromelina.

Attività farmacologica

Antiinfiammatorio, antiedematoso e antidolorifico. Spiccata attività proteolitica.

Impiego clinico

Cellulite. Ritenzione idrica. Diminuita attività pancreatica. Processi infiammatori ed edematosi in campo medico e chirurgico.

Controindicazioni

I preparati a base di gambo di Ananas dovrebbero essere utilizzati con estrema cautela in soggetti con ulcera peptica attiva.

Avvertenze e speciali precauzioni d'uso

Non sono noti studi clinici controllati in donne in gravidanza e durante l'allattamento in conformità con la prassi medica generale, il prodotto non deve essere utilizzato senza prima aver sentito il parere medico.

Interazioni

Possibili interazioni con anticoagulanti e inibitori dell'aggregazione piastrinica.

Effetti indesiderati

In alcuni casi sono stati segnalati lievi disturbi gastrointestinali.

Note Bibliografiche

Composizione

Il componente principale del gambo di Ananas è rappresentato dalla bromelina, che appare oramai come una famiglia di proteinasi (enzimi proteolitici), nella quale sono state identificate finora almeno 8 frazioni diverse[1]; sono inoltre presenti la comosaina e la ananaina, altre due cistein-proteinasi enzimaticamente molto vicine alla bromelina[2]. Altri composti minori sono gli acidi cinnamico, p-cumarico e ferulico[3]; polisaccaridi (glucuronoarabinoxilani e xiloglucani); piccole quantità di pectine e glucomannani (o galattoglucomannani)[4] vitamina C e fibre vegetali[5].

Attività biologiche ed impieghi clinici descritti in letteratura

Le attività biologiche e gli impieghi clinici descritti per l'*Ananas sativum* sono essenzialmente dovuti alla bromelina[6], una miscela di enzimi proteolitici sulfidrici dotata di numerose e importanti attività[7].

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1 "Crude bromelain extracts from pineapple stems were fractionated by two-step FPLC-cation-exchangechromatography. At least eight basic proteolytically active components were detected (…)." *(Harrach T, Eckert K, Schulze-Forster K, Nuck R, Grunow D, Maurer HR. Isolation and partial characterization of basic proteinases from stem bromelain. Journal of Protein Chemistry 1995; 14: 41-52).*

2 ***"A mixture of ananain (EC 3.4.22.31) and comosain purified from crude pineapple stem extract wasfound to contain numerous closely related enzyme forms…*** Structural and kinetic analyses revealed comosain to be closely related to stem bromelain (EC 3.4.22.32), whereas ananain differed markedly from both comosain and stem bromelain." *(Napper AD, Bennett SP, Borowski M, Holdridge MB, Leonard MJ, Rogers EE, Duan Y, Laursen RA, Reinhold B, Shames SL. Genzyme Corporation, Cambridge, MA 02139. Purification and characterization of multiple forms of the pineapple-stem-derived cysteine proteinases ananain and comosain. Biochemical Journal 1994; 301: 727-35).*

3 "Cinnamic, p-coumaric and ferulic acids were isolated from pineapple stems (Ananas comosus var. Cayenne)." *(Tawata S, Taira S, Kobamoto N, Zhu J, Ishihara M, Toyama S. Synthesis and antifungal activity of cinnamic acid esters. Bioscience, Biotechnology and Biochemistry 1996; 60: 909-10).*

4 "The polysaccharides of cell walls isolated from the fleshy, edible part of the fruit of the monocotyledonpineapple [Ananas comosus (L.) Merr.] (family Bromeliaceae) were analyzed chemically…**Glucuronoarabinoxylans were the major non-cellulosic polysaccharides in the pineapple cell walls. Xyloglucans were also present, together with small amounts of pectic polysaccharides and glucomannans (or galactoglucomannans)**. The large amounts of glucuronoarabinoxylans and small amounts of pecticpolysaccharides resemble the non cellulosic polysaccharide composition of the unlignified cell walls of the Poaceae." *(Smith BG, Harris PJ. Polysaccharide composition of unlignified cell walls of pineapple [Ananas comosus (L.) Merr.] fruit. Plant Physiology 1995; 107: 1399-409).*

5 "The sanitary quality of street sold fruits was analyzed during the period from march 1990 thru march 1993 in San Jose, Costa Rica… **The nutritional evaluation shows that fruit portions (except watermelon) satisfymore than 100% of the diary recommendation of vitamin C (60 mg) and 4-7% of the recommended ingestion of dietetic fiber (30g)**." *(Monge R, Arias ML, Antillon F, Utzinger D. Microbiological quality of street sold fruits in San Jose, Costa Rica. Archivos Latino americanos de Nutricion 1995; 45: 117-21).*

6 *Maurer HR. Bromelain: biochemistry, pharmacology and medical use. Cell Mol Life Sci. 2001 Aug;58(9):1234-45.*

7 "Effects of orally administered bromelain in an ovalbumin (OVA)-induced murine model of acute allergic airway disease (AAD). Oral bromelain significantly reduced BAL CD19+ B cells (P </= 0.0001) and CD8+ T cells (P </= 0.0001) in AAD mice when

Attività antiedematosa ed antinfiammatoria. L'attività antiedematosa ed antiinfiammatoria della bromelina è risultata evidente in diversi modelli sperimentali come l'edema da albumina, carragenina, destrano e lievito, edema traumatico, edema polmonare da adrenalina, asma da ovalbumina[8,9], dopo somministrazione sia orale che parenterale. Queste attività sono state confermate nel corso degli anni anche nell'uomo, dove la bromelina è risultata utile nel ridurre la componente infiammatoria ed edematosa in patologie diverse. In una sperimentazione clinica in doppio cieco, controllata con placebo, la somministrazione orale di bromelina ha dimostrato di ridurre l'edema flogistico secondario all'estrazione di un dente molare, in una percentuale variabile fra il 6 ed il 15%[10]. Recenti studi suggeriscono che la bromelina potrebbe essere efficace anche nel trattamento di patologie infiammatorie intestinali. In modelli sperimentali, Il trattamento con bromelina ha diminuito i segni clinici e istologici di coliti spontanee e di colon infiammato[11]. La bromelina risulta indicata, in generale per tutte le condizioni edematose e/o infiammatorie che coinvolgono i tessuti molli, quali p.e. edemi sottocutanei secondari a traumi articolari o muscolari tipo contusioni, strappi

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compared with controls". (*Secor ER, Carson WF, Singh A, Pensa M, Guernsey LA, Schramm CM, Thrall RS. Oral Bromelain Attenuates Inflammation in an Ovalbumin-induced Murine Model of Asthma. Evid Based Complement Alternat Med. 2008 Mar;5(1):61-9).*

8 "Determine the effect of bromelain treatment in an ovalbumin (OVA)-induced murine model of allergic airway disease (AAD). Mice were treated i.p. with either saline, 2 or 6 mg/kg bromelain, twice daily for four consecutive days. …Bromelain attenuated development of AAD while altering CD4+ to CD8+ T lymphocyte populations." *(Secor ER Jr, Carson WF 4th, Cloutier MM, Guernsey LA, Schramm CM, Wu CA, Thrall RS. Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murine model of allergic airway disease. Cell Immunol. 2005 Sep; 237(1):68-75).*

9 "A placebo-controlled double-blind study of 100 patients with impacted and/or dislocated lower wisdom teeth was conducted to examine the tolerance and antiphlogistic efficacy of bromelaine: a mixture of proteolytic enzymes from ananas comosus. Treatment was started 1 day prior to third molar surgery with a daily dose of 3x80 mg and was continued for a total of 6 days. **On the 1st day following surgery, linear measurement(distance: tragus-pogonion) showed swelling to be 7.5% lower under drug treatment than in the placebo group**. Two-dimensional image evaluation increased this difference to 15.9%, which however still failed to attain the significance level of 20%. Between the 3rd and the 7th postoperative day no differences were found between the two groups regarding the extent of soft tissue swelling or the speed of edema resolution." *(Hotz G, Frank T, Zoller J, Wiebelt H. Antiphlogistic effect of bromelaine following third molar removal. Deutsche Zahnarztliche Zeitschrift 1989; 44: 830-2).*

10 "Exposure to bromelain in vitro has been shown to remove a number of cell surface molecules that are vital to leukocyte trafficking, including CD128a/CXCR1 and CD128b/CXCR2 that serve as receptors for the neutrophil chemoattractant IL-8 and its murine homologues. Using an in vitro chemotaxis assay, we demonstrated a 40% reduction in migration of bromelain- vs. sham-treated human neutrophils in response to rhIL-8... In vivo bromelain treatment generated a 50-85% reduction in neutrophil migration in 3 different murine models of leukocyte migration into the inflamed peritoneal cavity." *(Fitzhugh DJ, Shan S, Dewhirst MW, Hale LP. Bromelain treatment decreases neutrophil migration to sites of inflammation. Clin Immunol. 2008 Jul; 128(1):66-74*).

11 "Platelet count decreased after incubation with 2.5 and 5 mg bromelain/ml from 277 +/- 17 platelets/nl before to 256 +/- 21 and 247 +/- 19 platelets/nl after the treatment. The ADP and TRAP-6 induced platelet aggregation led to a significant decrease after the incubation with 2.5 mg (ADP: 48.6 +/- 25.7%; TRAP-6: 49.6 +/- 28.9%) or 5 mg (ADP: 5.0 +/- 4.6%; TRAP-6: 9.0 +/- 4.9%) bromelain/ml in comparison to control (ADP: 81.4 +/- 5.0%; TRAP-6: 77.4 +/- 10.4%). The percentage of unstimulated CD62P positive platelets which were investigated by flow cytometry was minimally higher after incubation with 5 mg bromelain/ml (0.57 +/- 0.48% PC) in comparison to control (0.22 +/- 0.11% PC), but after TRAP-6 stimulation the incubation with 5 mg bromelain/ml led to a remarkable decrease in comparison to the untreated control (50.4 +/- 20.2 to 0.9 +/- 0.8% PC). The changes of CD62P (TRAP-stimulated) and the results of platelet aggregation after incubation with bromelain in vitro may demonstrate the potential of bromelain as a substance for platelet inhibition." *(Gläser D, Hilberg T. The influence of bromelain on platelet count and platelet activity in vitro. Platelets. 2006 Feb; 17(1):37-41).*

o stiramenti muscolari, nei casi di insufficienza venosa cronica ed altre situazioni di rallentato deflusso venoso (varici, varicoflebiti, ecc), negli interventi chirurgici (estrazioni dentarie, resezioni di lesioni cutanee, ecc). L'attività antinfiammatoria sembra essere legata ad una interazione della bromelina sulla lipo-ossigenasi, con il risultato di ridurre la sintesi di sostanze flogogene e ridurre la vasodilatazione, oltre che ad un incremento della depolimerizzazione della fibrina ed ad un'inibizione dell'aggregazione piastrinica[12]. Tutti questi fattori favoriscono il ripristino di una corretta permeabilità della parete vascolare (condizione alterata nell'infiammazione), favorendo così il riassorbimento del materiale edematoso e riducendone la stasi nei tessuti circostanti[13]. Inoltre la bromelina sembra essere molto efficace anche nel migliorare a funzionalità muscolare dopo intensa attività fisica[14]. Tra le varie applicazione della bromelina ci sono stati risultati promettenti ottenuti anche in un modello sperimentale di asma allergica acuta, indotta da ovalbumina per via intraperitoneale per tre giorni. L'effetto della bromelina ha prodotto una riduzione: della sensibilità

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[12] *Maurer HR. Bromelain: biochemistry, pharmacology and medical use. Cell Mol Life Sci. 2001 Aug; 58(9):1234-45.*

[13] "Protease supplementation has been purported to reduce the damaging effects of eccentric exercise and accelerate recovery of muscle function, possibly by regulating inflammation. To determine the effectiveness of protease supplementation in attenuating eccentric exercise-induced skeletal muscle damage and inflammation. After standard physical and hemodynamic assessment and fasting venous blood samples, subjects performed isokinetic extension/flexion of the quadriceps group on a Biodex isokinetic dynamometer at 60 degrees .s, followed by VO^2max testing. Subjects were randomly assigned to consume 5.83 g daily of either a cellulose placebo (N = 15; 22.27 +/- 3.33 yr, 71.17 +/- 2.91 inches, 179.4 +/- 24.05 lb, 50.55 +/- 5.66 mL.kg. min) or a proteolytic supplement containing fungal proteases, bromelain, and papain (N = 14; 22.85 +/- 5.9 yr, 70.0 +/- 2.67 inches, 173.11 +/- 29.94 lb, 49.69 +/- 6.15 mL.kg.min) for a period of 21 d. After the supplementation period, subjects donated blood samples before performing a 45-min downhill (-17.5%) treadmill protocol at 60% of VO^2max. An additional four blood draws and three muscle function tests were performed during the next 48 h. Blood was analyzed using standard hematology and clinical chemistry, enzyme-linked immunosorbent assay, and bead array. Blood data were analyzed using multivariate analysis of variance (MANOVA) with repeated measures, whereas Biodex data were analyzed using a MANOVA on %Delta values. Significant group differences (T1-T3, P = 0.033; T1-T4, P = 0.043) and another strong trend (T1-3 h, P = 0.055) were observed for flexion (peak torque %Delta at 60 degrees .s) indicating higher force production in the protease group. Significant group x time interactions (P < 0.05) were observed, including elevations in circulating eosinophils and basophils in the protease group coinciding with lower levels of serum cyclooxygenase 2, interleukin 6, and interleukin 12 in this group. Protease supplementation seems to attenuate muscle strength losses after eccentric exercise by regulating leukocyte activity and inflammation." *(Buford TW, Cooke MB, Redd LL, Hudson GM, Shelmadine BD, Willoughby DS. Protease Supplementation Improves Muscle Function after Eccentric Exercise. Med Sci Sports Exerc. 2009: 41(10):1908-1914.)*

[14] "Bromelain, a widely used pineapple extract with cysteine protease activity, has been shown to have immunomodulatory effects in a variety of immune system models. The purpose of the present study was to determine the effects of orally administered bromelain in an ovalbumin (OVA)-induced murine model of acute allergic airway disease (AAD). To establish AAD, female C57BL/6J mice were sensitized with intraperitoneal (i.p.) OVA/alum and then challenged with OVA aerosols for 3 days. Mice were gavaged with either (phosphate buffered saline) PBS or **200 mg/kg bromelain** in PBS, twice daily for four consecutive days, beginning 1 day prior to OVA aerosol challenge. Airway reactivity and methacholine sensitivity, bronchoalveolar lavage (BAL) cellular differential, Th2 cytokines IL-5 and IL-13, and lung histology were compared between treatment groups. Oral bromelain-treatment of AAD mice demonstrated therapeutic efficacy as evidenced by decreased methacholine sensitivity (P </= 0.01), reduction in BAL eosinophils (P </= 0.02) and IL-13 concentrations (P </= 0.04) as compared with PBS controls. In addition, oral bromelain significantly reduced BAL CD19+ B cells (P </= 0.0001) and CD8+ T cells (P </= 0.0001) in AAD mice when compared with controls. These results suggest that **oral treatment with bromelain had a beneficial therapeutic effect in this murine model of asthma and bromelain may also be effective in human conditions**." *(Secor ER, Carson WF, Singh A, Pensa M, Guernsey LA, Schramm CM, Thrall RS. Oral Bromelain Attenuates Inflammation in an Ovalbumin-induced Murine Model of Asthma. Evid Based Complement Alternat Med. 2008 Mar; 5(1):61-9.)*

alla metacolina, del numero di eosinofili nel lavaggio broncoalveolare e dei livelli di una citochina nota come Interleuchina 13 (IL-13) rispetto al placebo[15]. In uno studio clinico controllato condotto in Germania, è stata indagata l'efficacia della bromelina in bambini (età < 11anni) affetti da sinusite. Il parametro valutato è stato quello del tempo di scomparsa dei sintomi, e si è visto che la bromelina da sola portava alla scomparsa dei sintomi dopo circa 6 giorni rispetto a 7-8 giorni nei pazienti trattati con la terapia standard rispetto anche ai 9 giorni dei pazienti tratti con la combinazione della bromelina e terapia standard. Questo studio indica che la bromelina possa essere indicata anche nel trattamento della sinusite nei bambini[16]. In uno studio randomizzato verso un controllo condotto in doppio cieco, la bromelina ha favorito la riduzione di edema ed ecchimosi in pazienti sottoposti ad intervento chirurgico di rinoplastica[17]. La bromelina risulta particolarmente vantaggiosa in quei soggetti che presentano controindicazioni all'uso o una scarsa tollerabilità nei confronti di farmaci antiinfiammatori non steroidei, o nei quali l'uso di antiinfiammatori steroidei possa apparire sproporzionato rispetto all'entità del processo infiammatorio ed edematoso. In uno studio clinico controllato è stato valutato l'effetto della bromelina in pazienti affetti da osteoartrite del ginocchio

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15 "The therapeutic efficiency and safety of the proteolytic enzyme bromelaine obtained from pineapple (Bromelain-POS, Ursapharm GmbH, Saarbrücken, Germany) was evaluated in children under the age of 11 years diagnosed with acute sinusitis. Data from 116 patients from 19 centres located across Germany were analysed in a pharmacoepidemiological cohort study. Patient cohorts were either treated with Bromelain-POS (N = 62), in combination with Bromelain-POS and standard therapies (N = 34), or with standard therapies (N = 20). The primary parameter measuring effectiveness of the different treatment groups was the duration of symptoms. The shortest mean period of symptoms was observed in patients treated with **Bromelain-POS alone (6.66 days), followed by the standard therapy (7.95 days) and those treated with a combination of Bromelain-POS and the standard therapy (9.06 days).** Patients of the Bromelain-POS monotherapy group showed a statistically significant faster recovery from symptoms (p = 0.005) compared to the other treatment groups. One 10-year-old male patient, with a known pineapple allergy, showed a self-limiting mild allergic reaction. No other unwanted side-effects were reported. This trial documents that the proteolytic pineapple **enzyme Bromelain-POS is widely used in the treatment of young children diagnosed with acute sinusitis in Germany and that the use of proteolytic enzymes can benefit such patients**." *(Braun JM, Schneider B, Beuth HJ. Therapeutic use, efficiency and safety of the proteolytic pineapple enzyme Bromelain-POS in children with acute sinusitis in Germany. In Vivo. 2005 Mar-Apr; 19(2):417-21.)*

16 *Seltzer A.P.A double-blind study of bromelains in the treatment of edema and ecchymoses following surgical and nonsurgical trauma to the face. Eye Ear Nose Throat Mon. 1964 Oct; 43:54-7.*

17 "Osteoarthritis (OA) of the knee is the most prevalent joint disorder. Previous studies suggest that bromelain, a pineapple extract, may be a safer alternative/adjunctive treatment for knee OA than current conventional treatment. AIM: To assess the efficacy of bromelain in treating OA of the knee. Randomized, double-blind placebo-controlled trial. Subjects (n = 47) with a confirmed diagnosis of moderate to severe knee OA were randomized to 12 weeks of bromelain 800 mg/day or placebo, with a 4-week follow-up. Knee (pain, stiffness and function) and quality-of-life symptoms were reported monthly in the WOMAC and SF36 questionnaires, respectively. Adverse events were also recorded. The primary outcome measure was the change in total WOMAC score from baseline to the end of treatment at week 12. Longitudinal models were used to evaluate outcome. Thirty-one patients completed the trial (14 bromelain, 17 placebo). No statistically significant differences were observed between groups for the primary outcome (coefficient 11.16, p = 0.27, 95%CI -8.86 to 31.18), nor the WOMAC subscales or SF36. Both treatment groups showed clinically relevant improvement in the WOMAC disability subscale only. Adverse events were generally mild in nature. This study suggests that bromelain is not efficacious as an adjunctive treatment of moderate to severe OA, but its limitations support the need for a follow-up study. " *(Brien S, Lewith G, Walker AF, Middleton R, Prescott P, Bundy R. Bromelain as an adjunctive treatment for moderate-to-severe osteoarthritis of the knee: a randomized placebo-controlled pilot study. QJM. 2006 Dec; 99(12):841-50.)*

con il risultato di non essere efficace[18].

Cellulite, obesità e sovrappeso. Un uso peculiare e diffuso del gambo d'Ananas è conosciuto nel trattamento della cellulite. È noto, infatti, come una eccessiva ritenzione idrosalina nei tessuti sottocutanei contribuisca, insieme al deposito di lipidi nel tessuto adiposo, alla patogenesi della cellulite e alla formazione della cosiddetta "buccia d'arancia", un'alterazione della normale morfologia cutanea tipica della cellulite. Attraverso una rimozione dell'acqua e dei sali accumulatisi nel tessuto sottocutaneo ed una stimolazione della diuresi, il gambo d'Ananas può agevolare il ripristino di un normale trofismo cutaneo e la scomparsa delle lesioni tipiche della cellulite. Per gli stessi motivi, l'Ananas è spesso inserito nelle diete ipocaloriche di soggetti obesi o in sovrappeso, specialmente quando si sospetta che una ritenzione idrica possa contribuire all'aumento del peso corporeo.

Attività sulle ferite e sulle ustioni. Le cistein-proteinasi presenti nell'*Ananas comosus* sono state utilizzate con successo nella pulizia di ferite e di ustioni. In un modello di ustione sperimentale nel ratto, l'applicazione di proteinasi 24 ore dopo l'induzione della lesione ha determinato una completa pulizia dei tessuti, e gli AA. suggeriscono l'uso dell'ananas in sostituzione della pulizia chirurgica[19]. L'attività è stata osservata anche in ustioni nell'uomo, dove il trattamento con bromelina comporta – oltre ad una accurata pulizia della lesione – anche una riduzione del dolore[20]. Questi dati sono stati confermati anche in uno studio preliminare condotto in 130 pazienti con bruciature di secondo e terzo stadio valutando l'efficacia di un prodotto commerciale contenente bromelina.

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[18] "A limited in vivo study using 12 rats with full-thickness skin burns injuries was carried out. The animals were treated 24 h post burn with two newly discovered enzyme fractions derived from the stem of the pineapple (Ananas comosus). **The results indicated that even debridement of the injury could be effected rapidly (within 4 h)**. Although the details of enzyme formulation and clinical application have yet to be established, these findings clearly suggest that two enzyme fractions from pineapple stem have potential as non-surgical debriding agents." *(Rowan AD, Christopher CW, Kelley SF, Buttle DJ, Ehrlich HP. Debridement of experimental full-thickness skin burns of rats with enzyme fractions derived from pineapple stem. Burns 1990; 16: 243-6).*

[19] "In an open case observation study involving patients with blunt injuries to the musculoskeletal system, the efficacy and tolerability of high-dose Bromelain POS, a plant-derived enzyme preparation, were investigated. The investigating physician was an orthopedic surgeon who, in addition to the usual therapeutic measures, treated 59 of his patients with the bromelaine preparation. The duration of the application was determined by the nature and severity of the lesion, and varied between one and three weeks. The test criteria were swelling, pain at rest and during movement, and tenderness. These parameters were evaluated on the day of the injury and on five subsequent dates. **Treatment with bromelaine resulted in a clear reduction in all four parameters tested. Both swelling and the symptoms of pain had improved appreciably at all evaluation time points as compared with baseline.** The tolerability of the preparation was very good, and patient compliance was correspondingly high." *(Masson M. Bromelain in blunt injuries of the locomotors system. A study of observed applications in general practice. Fortschritte der Medizin 1995; 113: 303-6).*

[20] "Debridase was applied after saturating the burns with a moist dressing for 2-24h. **Debridase was applied for a period of 4h under an occlusive dressing.** Mean patient age was 18.6 +/- 19.3, 42 (32.3%) were female, and 63 (48.5%) were children under age 18. Most burns were small. Debridase was applied once in 241 (72.6%) of the 332 wounds, twice in 67 (20.18%) cases, three times in 12 (3.61%) cases, and four times in 2 (0.6%) cases. **The percentage debridement by number of applications was 89 +/- 21% for a single application, 77 +/- 27% for two, and 62 +/- 27% for three Debridase applications, respectively**. There were no significant adverse events. **The availability of a fast acting, reliable and complication-free enzymatic debriding agent may open new horizons and provide a new treatment modality for burns**." *(Rosenberg L, Lapid O, Bogdanov-Berezovsky A, Glesinger R, Krieger Y, Silberstein E, Sagi A, Judkins K, Singer AJ. Safety and efficacy of a proteolytic enzyme for enzymatic burn debridement: a preliminary report. Burns. 2004 Dec; 30(8):843-50.)*

La preparazione topica è stata applicata per 4 ore in occlusione (attraverso l'impiego di un cerotto). La percentuale di rimozione di tessuti morti, danneggiati o infetti, che potrebbero altrimenti compromettere la guarigione della lesione è stata dell'89% dopo una singola applicazione, del 77% dopo due applicazioni e del 62% dopo la terza[21].

Altre attività. La bromelina è stata investigata in un piccolo studio clinico, otto pazienti affetti da pitiriasi lichenoide cronica, che di per sé non è una malattia molto frequente e di origine non bene nota, ma spesso riguarda l'età pediatrica[22]. Dopo tre mesi di trattamento orale con bromelina è stata ottenuta una completa risoluzione clinica. Si trovano in commercio integratori alimentari a base di bromelina, che favorirebbero la digestione degli alimenti proteici[23]. Studi recenti indicano che la bromelina possiede effetti antitumorali, infatti in alcuni modelli sperimentali sembra interferire con la replicazione e la crescita di cellule maligne[24,25]. La bromelina in ultimo, sembra esercitare un

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21 "The aim of the present study was to evaluate the efficacy of bromelain, a crude aqueous extract of the stems and immature fruit of pineapple, in the treatment of PLC. Eight patients (3 males and 5 females) with PLC were enrolled in the study and **treated for three months with oral bromelain (40 mg 3 times a day for 1 month, 40 mg twice a day for 1 month and 40 mg/day for 1 month).** All patients showed complete clinical recovery after treatment. In 12 months of follow up, two patients experienced relapse 5-6 months after suspension of therapy but responded to another brief cycle of therapy. No side effects were encountered during therapy. In conclusion bromelain can be considered an effective therapeutic option for PLC; **its efficacy could be related to its anti-inflammatory, immunomodulatory and/or anti-viral properties**." *(Massimiliano R, Pietro R, Paolo S, Sara P, Michele F. Role of bromelain in the treatment of patients with pityriasis lichenoides chronica. J Dermatolog Treat. 2007; 18(4):219-22.).*

22 *Roxas M. The role of enzyme supplementation in digestive disorders. Altern Med Rev. 2008 Dec; 13(4):307-14.*

23 "Bromelain treatment resulted in upregulation of p53 and Bax and subsequent activation of caspase 3 and caspase 9 with concomitant decrease in Bcl-2. A marked inhibition in cyclooxygenase-2 (Cox-2) expression and inactivation of nuclear factor-kappa B (NF-kappaB) was recorded, as phosphorylation and consequent degradation of I kappa B alpha was blocked by bromelain. Also, bromelain treatment curtailed extracellular signal regulated protein kinase (ERK1/2), p38 mitogen-activated protein kinase (MAPK) and Akt activity. The basis of anti tumor-initiating activity of bromelain was revealed by its time dependent reduction in DNA nick formation and increase in percentage prevention. Thus, modulation of inappropriate cell signaling cascades driven by bromelain is a coherent approach in achieving chemoprevention." *(Bhui K, Prasad S, George J, Shukla Y. Bromelain inhibits COX-2 expression by blocking the activation of MAPK regulated NF-kappa B against skin tumor-initiation triggering mitochondrial death pathway. Cancer Lett. 2009 Sep 18; 282(2):167-76).*

24 "The antitumor and antimetastatic activities of the plant cysteine endoproteinase bromelaine were evaluated in a murine model. Syngeneic sarcoma L-1 cells were incubated with bromelaine (after preceeding time and dosage kinetics) and subcutaneously; (s.c.) or intravenously; (i.v.) inoculated into BALB/c-mice (n = 5 per experimental group) to induce local tumor growth or lung colonization. Compared to non-protease incubated L-1 cells, local tumor growth and experimental lung metastasis decreased significantly ($p < 0.05$). After bromelaine incubation of the tumor cells. Sarcoma L-1 cells induced local tumor growth after s.c. inoculation and lung colonization after i.v. injection. Intraperitoneal (i.p.) or s.c. administration of bromelaine (optimal dosage and time schedule tested in preceeding kinetic studies) significantly ($p < 0.05$) reduced local tumor weight, however, lung colonization was non-significantly reduced. Bromelaine incubation of sarcoma L-1 cells significantly reduced their tumorigenic/metastatic capacities. Bromelaine treatment after tumor cell inoculation significantly reduced local tumor growth, experimental lung metastasis, however, to a lesser, non-significant degree." *(Beuth J, Braun JM. Modulation of murine tumor growth and colonization by bromelaine, an extract of the pineapple plant (Ananas comosum L.). In Vivo. 2005 Mar-Apr; 19(2):483-5.)*

25 "The antitumor and antimetastatic activities of the plant cysteine endoproteinase bromelaine were evaluated in a murine model. Syngeneic sarcoma L-1 cells were incubated with bromelaine (after preceeding time and dosage kinetics) and subcutaneously; (s.c.) or intravenously; (i.v.) inoculated into BALB/c-mice (n = 5 per experimental group) to induce local tumor growth or lung colonization. Compared to non-protease incubated L-1 cells, local tumor growth and experimental lung metastasis decreased significantly ($p < 0.05$). After bromelaine incubation of the tumor cells. Sarcoma L-1 cells induced local tumor growth after s.c.

effetto cardioprotettivo, ma il dato è ancora solo sperimentale[26].

Tollerabilità. I preparati a base di gambo di Ananas risultano controindicati in soggetti con ulcera peptica attiva. In alcuni casi sono stati segnalati lievi disturbi gastrointestinali. La bromelina ha una moderata attività antiaggregante piastrinica ed interagisce con alcuni fattori della coagulazione, per cui è possibile un prolungamento del tempo di emorragia in soggetti con diatesi emorragica o in pazienti in trattamento con anticoagulanti o antiaggreganti piastrinici, anche se attualmente è stato pubblicato un report sulla sicurezza che ne riconosce un utilizzo abbastanza sicuro alle dosi raccomandate[27].

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inoculation and lung colonization after i.v. injection. Intraperitoneal (i.p.) or s.c. administration of bromelaine (optimal dosage and time schedule tested in preceeding kinetic studies) significantly ($p < 0.05$) reduced local tumor weight, however, lung colonization was non-significantly reduced. Bromelaine incubation of sarcoma L-1 cells significantly reduced their tumorigenic/metastatic capacities. Bromelaine treatment after tumor cell inoculation significantly reduced local tumor growth, experimental lung metastasis, however, to a lesser, non-significant degree." *(Beuth J, Braun JM. Modulation of murine tumor growth and colonization by bromelaine, an extract of the pineapple plant (Ananas comosum L.). In Vivo. 2005 Mar-Apr; 19(2):483-5.)*

[26] "Bromelain (Br), a proteolytic enzyme extracted from the stem of the pineapple, is known to possess anti-inflammatory activity and **has been shown to reduce blood viscosity, prevent the aggregation of blood platelets, and improve ischemia-reperfusion (I/R) injury in a skeletal muscle model.** We investigated the capacity of Br to limit myocardial injury in a global I/R model. Adult male Sprague-Dawley rats were divided into two groups: control (PBS) and Br at 10 mg/kg in PBS administered via intraperitoneal injection (twice/day) for 15 consecutive days. On day 16, the hearts were excised and subjected to 30 min of global ischemia followed by 2 h of reperfusion. Br treatment showed higher left ventricular functional recovery throughout reperfusion compared with the controls [maximum rate of rise in intraventricular pressure (dP/dt max), 2,225 vs. 1,578 mmHg/s at 2 h reperfusion]. Aortic flow was also found to be increased in Br treatment when compared with that in untreated rats (11 vs. 1 ml). Furthermore, Br treatment reduced both the infarct size (34% vs. 43%) and the degree of apoptosis (28% vs. 37%) compared with the control animals. Western blot analysis showed an increased phosphoryla-tion of both Akt and FOXO3A in the treatment group compared with the control. **These results demonstrated for the first time that Br triggers an Akt-dependent survival pathway in the heart, revealing a novel mechanism of cardioprotective action and a potential therapeutic target against I/R injury.**" *(Juhasz B, Thirunavukkarasu M, Pant R, Zhan L, Penumathsa SV, Secor ER Jr, Srivastava S, Raychaudhuri U, Menon VP, Otani H, Thrall RS, Maulik N. Bromelain induces cardioprotection against ischemia-reperfusion injury through Akt/FOXO pathway in rat myocardium. Am J Physiol Heart Circ Physiol. 2008 Mar; 294(3):H1365-70.)*

[27] "Medicinal qualities of bromelain include anti-inflammatory, anti-thrombotic, fibrinolytic and anti-cancer functions. Existing evidence derived from clinical observations as well as from mouse- and cell-based models suggests that bromelain acts systemically, affecting multiple cellular and molecular targets. In recent years, studies have shown that bromelain has the capacity to modulate key pathways that support malignancy. It is now possible to suggest that the anti-cancer activity of bromelain consists in the direct impact on cancer cells and their micro-environment, as well as in the modulation of immune, inflammatory and haemostatic systems. This review will summarize existing data relevant to bromelain's anti-cancer activity and will suggest mechanisms which account for bromelain's effect, in the light of research involving non-cancer models." *(Orsini R.A. Bromelain. Plast. Reconstr. Surg. 2006;118:1640-1644).*