Gli effetti terapeutici della Bromelina

Davide Allegri

Consulente scientifico

NUTRITIONAL ACADEMY

Premessa

La bromelina è un enzima di notevole interesse scientifico. Sempre più numerosi studi evidenziano un suo possibile ampio utilizzo in ambito terapeutico. I molteplici effetti positivi registrati in vitro e in vivo fanno sì che questa sostanza naturale sia di estrema utilità nella gestione di determinate patologie.

- La bromelina facilita e velocizza il **riequilibrio dei mediatori dell'infiammazione**, condizione necessaria per mantenere in salute l'organismo. [3]
- Presenta un ampio raggio di utilizzo, ma il suo effetto clinico più rilevante è l'**antinfiammatorio**. [4]

È appurato come **l'infiammazione cronica sia associata alla presenza di diverse patologie**, anche gravi, favorendone l'insorgenza e lo sviluppo. [5,6]

Vediamo quindi sinteticamente quali sono gli effetti della bromelina secondo le evidenze scientifiche e cliniche, da studi in vitro e su modelli sperimentali.

Effetto antinfiammatorio

- **Riduce COX-2** e **PGE-2** [7]
- **Stimola IL-1, TNF, IL-6 e INF** [8-10]
- **Riduce la secrezione di IL-1, TNF e IL-6** in caso di eccessiva produzione di citochine [11,12]
- **Diminuisce la presenza della Sostanza P e di PGE-2 nell'essudato** [13]
- **Remissione clinica ed endoscopica della colite ulcerosa** [14]
- **Modula l'espressione di CD44** [15,16]
- **Modula l'espressione del TGF nell'artrite reumatoide** e nella **osteomielofibrosi** [17,18]
- **Attiva le cellule Natural Killer** e **aumenta la secrezione di Il-2**. **Riduce le cellule T-helper**. [19,20]

COX= ciclossigenasi; PGE= prostaglandina; IL= interleuchina; TNF= Tumor Necrosis Factor; INF= Interferone; TGF= Transforming Growth Factor.

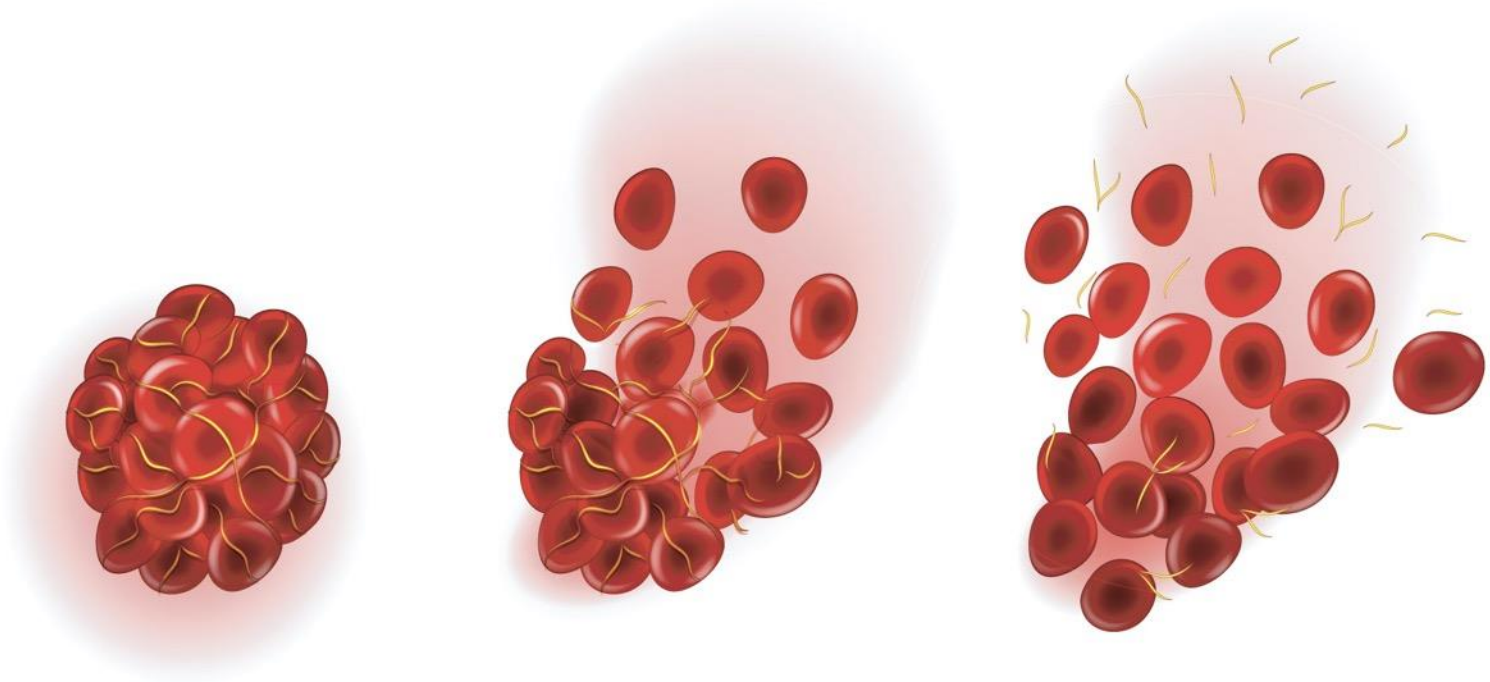
NUTRITIONAL ACADEMY

Effetto antineoplastico

Cancro al seno	• Agisce come agente antitumorale • Inibisce la crescita delle cellule MFC-7, induce l'apoptosi [21] • Un aumento del dosaggio di Bromelina facilita l'apoptosi [22]
Melanoma	• Riduce la proliferazione delle cellule tumorali e riduce l'espressione di COX-2 [23] • Induce l'apoptosi e riduce le cellule metastatiche [24] • Riduce il fattore CD44 [25]
Cancro pancreatico	• Migliora l'efficacia dei chemioterapici [26] (SPRA-Bromelain). [27]

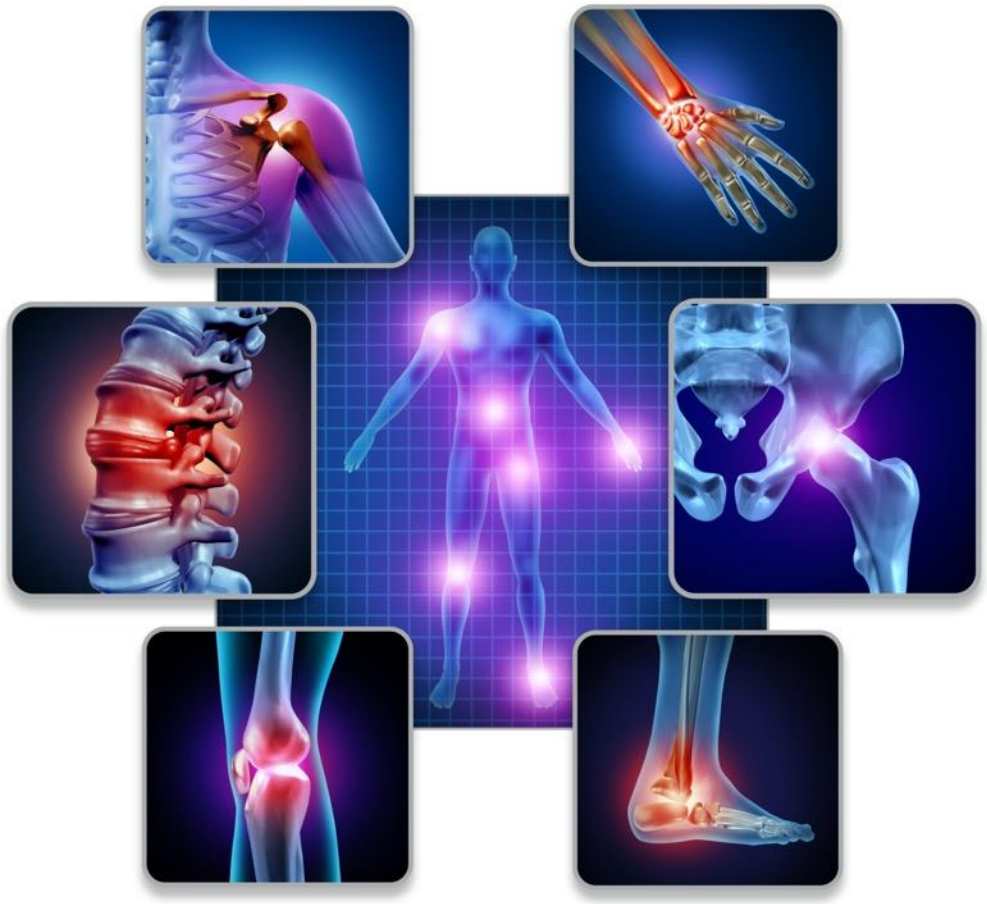
Effetto fibrinolitico

- Induce la fibrinolisi e riduce la capacità coagulante [34]
- Riduce la concentrazione ematica di fibrina [35]
- Riduce la pre-callicreina, il fattore X, la protrombina e inibisce la produzione di bradichinina. [36]



La Bromelina nel trattamento dell'osteoartrosi

- Svolge effetto analgesico [28,29]
- Mostra effetti simili ai FANS, ma con effetti collaterali molto ridotti [30,31]
- In sinergia con Tripsina e Rutina, consente di ottenere risultati clinici sovrapponibili al Diclofenac. [30,32,33]



Altri effetti terapeutici

Effetto	Meccanismo d'azione
Effetto antimicrobico	• Limita la proliferazioni di batteri dannosi per l'intestino (Escherichia coli e Vibrio Cholera) [37]
Effetto antiplacca	• Agente antiplacca [38]
Effetto analgesico	• Riduce il dolore post operatorio e da artrosi [39-41]
Effetto antiossidante	• Stimola la secrezione degli enzimi antiossidanti [42]
Effetti sulle ferite	• Riduce l'edema [43-45] • Abbrevia i tempi di guarigione [46]
Effetto sull'assorbimento degli antibiotici	• Migliora la permeabilità e l'assorbimento degli antibiotici. [47-49] • Migliora l'efficacia degli antibiotici e ne riduce gli effetti collaterali [50]
Trattamento delle sinusiti	• Migliora la sintomatologia [50] • Riduce la produzione delle prostaglandine e il gonfiore delle vie nasali. [24]

In sintesi gli studi più rilevanti condotti sull'uomo

Campo di studio	Soggetti	Dosaggio	Outcomes	Ref.
Attività antinfiammatoria	25 pazienti	160 mg/die	Riduzione della sintomatologia infiammatoria	51
Trattamento dell'osteoartrosi	29 pazienti con artrosi moderata o severa	60-160 mg/die	Riduzione del gonfiore nel 72,4% dei pazienti	52
	60 pazienti	540 mg/die	Effetto su diversi parametri relativi a dolore e disfunzione	18
	73 pazienti	540 mg/die	Riduzione del dolore secondo la scala Lequesne	53
	50 pazienti	1890 mg/die	Valutazione del dolore e funzione secondo scala Likert	54
Trattamento delle ferite operatorie	80 pazienti	n.p.	Dolore ed edema significativamente ridotti	55
Trauma	59 pazienti	n.p.	Riduzione del dolore, gonfiore e tempi di recupero ridotti	56
Odontoiatria	45 pazienti	4 x 250 mg/die	Riduzione dell'infiammazione, gonfiore e dolore	40
Anti edemigeno	47 pazienti	20 mg/die	Tempo medio di sanguinamento leggermente ridotto	57

Conclusioni

Gli studi clinici citati evidenziano il grande e giustificato interesse dimostrato dal mondo medico-scientifico per la bromelina.

La sua efficacia terapeutica, sommata agli effetti collaterali estremamente ridotti, fa della bromelina una sostanza sicura che offre benefici quando viene utilizzata sia in sinergia con altri trattamenti, sia in somministrazione singola.

Bibliografia

1. Heinicke RM, Gortner WA. Stem bromelain—A new protease preparation from pineapple plants. Econ. Bot. 1957; 11: 225–234.
2. Chakraborty AJ, et al. Bromelain a Potential Bioactive Compound: A Comprehensive Overview from a Pharmacological Perspective. *Life (Basel)*. 2021; 11(4): 317.
3. Taussig SJ. The mechanism of the physiological action of bromelain. Med. Hypotheses 1980; 6: 99–104.
4. Rathnavelu V, et al. Potential role of bromelain in clinical and therapeutic applications (Review). Biomed. Rep. 2016; 5: 283–288.
5. Rahaman MM, et al. The genus curcuma and inflammation: Overview of the pharmacological perspectives. Plants. 2021;10: 63.
6. Huang JR, et al. Bromelain inhibits lipopolysaccharide-induced cytokine production in human THP-1 monocytes via the removal of CD14. Immunol. Investig. 2008; 37: 263–277.
7. Emran TB, et al. Effects of organic extracts and their different fractions of five Bangladeshi plants on in vitro thrombolysis. BMC Complement. Altern. Med. 2015; 15: 128.
8. Engwerda CR et al. Bromelain activates murine macrophages and natural killer cells in vitro. Cell. Immunol. 2001; 210: 5–10.
9. Engwerda CR et al. Bromelain modulates T cell and B cell immune responses in vitro and in vivo. Cell. Immunol. 2001; 210: 66–75.
10. Barth H, et al. In vitro study on the immunological effect of bromelain and trypsin on mononuclear cells from humans. Eur. J. Med. Res. 2005; 10: 325–331.
11. Hale LP, et al. Treatment with oral bromelain decreases colonic inflammation in the IL-10-deficient murine model of inflammatory bowel disease. Clin. Immunol. 2005; 116: 135–142.
12. Onken JE, et al. Bromelain treatment decreases secretion of pro-inflammatory cytokines and chemokines by colon biopsies in vitro. Clin. Immunol. 2008; 126: 345–352.
13. Gaspani L, et al. In vivo and in vitro effects of bromelain on PGE2 and SP concentrations in the inflammatory exudate in rats. Pharmacology. 2002; 65: 83–86.
14. Kane S, Goldberg MJ. Use of bromelain for mild ulcerative colitis. Ann. Intern. Med. 2000; 132: 680.
15. Rahman MA, et al. Antioxidative, antimicrobial and cytotoxic effects of the phenolics of Leea indica leaf extract. Saudi J. Biol. Sci. 2013; 20: 213–225.
16. Subramaniam V, et al. Soluble CD44 secretion contributes to the acquisition of aggressive tumor phenotype in human colon cancer cells. Exp. Mol. Pathol. 2007; 83: 341–346.

17. Bierie B, Moses HL. Tumour microenvironment—TGFB: The molecular Jekyll and Hyde of cancer. Nat. Rev. Cancer. 2006; 6: 506–520.
18. Leipner J, et al. Therapy with proteolytic enzymes in rheumatic disorders. BioDrugs. 2001; 15: 779–789.
19. Moss JN, et al. the Pharmacology of the Enzymes. Arch. Int. Pharmacodyn. Thérapie. 1963; 145: 166–189.
20. Giacca S. Clinical Experiences on the Action of Bromelin in Peripheral Venous Diseases and in Chronic Bronchitic States. Minerva Med. 1964; 55: 3925–3928.
21. Bhui, K.; Tyagi, S.; Prakash, B.; Shukla, Y. Pineapple bromelain induces autophagy, facilitating apoptotic response in mammary carcinoma cells. BioFactors 2010, 36, 474–482.
22. Dhandayuthapani, S.; Perez, H.D.; Paroulek, A.; Chinnakkannu, P.; Kandalam, U.; Jaffe, M.; Rathinavelu, A. Bromelain-induced apoptosis in GI-101A breast cancer cells. J. Med. Food 2012, 15, 344–349.
23. Bhui, K.; Tyagi, S.; Srivastava, A.K.; Singh, M.; Roy, P.; Singh, R.; Shukla, Y. Bromelain inhibits nuclear factor kappa-B translocation,driving human epidermoid carcinoma A431 and melanoma A375 cells through G 2/M arrest to apoptosis. Mol. Carcinog. 2012, 51, 231–243.
24. Manzoor, Z.; Nawaz, A.; Mukhtar, H.; Haq, I. Bromelain: Methods of Extraction, Purification and Therapeutic Applications. Brazilian Arch. Biol. Technol. 2016, 59.
25. Harrach T, et al. Bromelain proteinases modulate the cd44 expression on human molt-4/8 leukemia and sk-mel-28 melanoma-cells in-vitro. Int. J. Oncol. 1994; 5: 485–488.
26. Pillai K, et al. Enhancing the potency of chemotherapeutic agents by combination with bromelain and N-acetylcysteine—An in vitro study with pancreatic and hepatic cancer cells. Am. J.Transl. Res. 2020; 12: 7404–7419.
27. Higashi T, et al. Efficient Anticancer Drug Delivery for Pancreatic Cancer Treatment Utilizing Supramolecular Polyethylene-Glycosylated Bromelain. ACS Appl. Bio Mater. 2020; 3: 3005–3014.
28. Bodi T. The Effects of Oral Bromelains on Tissue Permeability to Antibiotics and Pain Response to Bradykinin: Double Blind Studies on Human Subjects. Clin. Med. 1966; 73: 61–65.
29. Kumakura S, et al. Effect of bromelain on kaolin-induced inflammation in rats. Eur. J. Pharmacol. 1988; 150: 295–301.
30. Pavan R, et al. Properties and Therapeutic Application of Bromelain: A Review. Biotechnol. Res. Int. 2012; 2012: 976203.

31. Brien S, et al. Bromelain as a Treatment for Osteoarthritis: A Review of Clinical Studies. Evid. Based Complement. Altern. Med. 2004; 1: 251–257.
32. Akhtar NM, et al. Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee—A double-blind prospective randomized study. Clin. Rheumatol. 2004; 23: 410–415.
33. Ueberall MA, et al. Efficacy, tolerability, and safety of an oral enzyme combination vs diclofenac in osteoarthritis of the knee: results of an individual patient-level pooled reanalysis of data from six randomized controlled trials. *J Pain Res*. 2016; 9: 941-961.
34. Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application. An update. J. Ethnopharmacol. 1988; 22: 191–203.
35. Rakib A, et al. Pharmacological studies on the antinociceptive, anxiolytic and antidepressant activity of Tinospora crispa. Phytother. Res. 2020; 34: 2978–2984.
36. Kelly GS. Bromelain: A literature review and discussion of its therapeutic applications. Altern. Med. Rev. 1996; 1: 243–257.
37. Mynott TL et al. Bromelain, from pineapple stems, proteolytically blocks activation of extracellular regulated kinase-2 in T cells. J. Immunol. 1999; 163: 2568–2575.
38. Harmely F, et al. Efektifitas Bromelain Kasar dari Batang Nenas (Ananas comosus L. Merr) sebagai Antiplak dalam Pasta Gigi. Sci. J. Farm. Dan Kesehat. 2015; 1: 14.
39. Golezar S. Ananas comosus effect on perineal pain and wound healing after episiotomy: A randomized double-blind placebo controlled clinical trial. Iran. Red Crescent Med. J. 2016; 18.
40. Majid OW, Al-Mashhadani BA. Perioperative bromelain reduces pain and swelling and improves quality of life measures after mandibular third molar surgery: A randomized, double-blind, placebo-controlled clinical trial. J. Oral Maxillofac. Surg. 2014; 72: 1043–1048.
41. Walker AF, et al. Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults. Phytomedicine. 2002; 9: 681–686.
42. Bakare AO, Owoyele BV. Antinociceptive and neuroprotective effects of bromelain in chronic constriction injury-induced neuropathic pain inWistar rats. Korean J. Pain 2020; 33: 13–22.
43. Howat RCL, Lewis GD. The Effect of Bromelain Therapy on Episiotomy Wounds—A Double Blind Controlled Clinical Trial. BJOG Int. J. Obstet. Gynaecol. 1972; 79: 951–953.
44. Singer AJ, et al. Rapid and selective enzymatic debridement of porcine comb burns with bromelain-derived Debrase®: Acute-phase preservation of noninjured tissue and zone of stasis. J. Burn Care Res. 2010; 31: 304–309.
45. Krieger Y, et al. Escharotomy using an enzymatic debridement agent for treating experimental burn-induced compartment syndrome in an animal model. J. Trauma Inj. Infect. Crit. Care 2005; 58: 1259–1264.

46. Rosenberg L, et al. Safety and efficacy of a proteolytic enzyme for enzymatic burn debridement: A preliminary report. Burns 2004.
47. Renzini G, Varengo M. Absorption of tetracycline in presence of bromelain after oral administration. Arzneimittel-Forschung/Drug Res. 1972; 22: 410–412
48. Bradbrook I, et al. The effect of bromelain on the absorption of orally administered tetracycline. Br. J. Clin. Pharmacol. 1978; 6: 552–554.
49. Tinozzi S, Venegoni A. Effect of bromelain on serum and tissue levels of amoxycillin. Drugs Exp. Clin. Res. 1978
50. Dighe NS, et al. Bromelain A Wonder Supplement: A Review. Pharmacologyonline 2010; 1: 11–18.
51. Seligman B. Bromelain: An anti-inflammatory agent. Angiology 1962; 13: 508–510.
52. Cohen A, Goldman J. Bromelains Therapy in Rheumatoid Arthritis. Pa. Med. J. 1964; 67: 27–30.
53. Klein G, Kullich W. Short-term treatment of painful osteoarthritis of the knee with oral enzymes. A randomised, double-blind study versus diclofenac. Clin. Drug Investig. 2000; 19: 15–23.
54. Tilwe GH, et al. Efficacy and Tolerability of Oral Enzyme Therapy as Compared to Diclofenac in Active Osteoarthrosis of Knee Joint: An Open Randomized Controlled Clinical Trial. J. Assoc. Physicians India. 2001
55. Ordesi P, et al. Therapeutic efficacy of bromelain in impacted third molar surgery: A randomized controlled clinical study. Quintessence Int. 2014; 45: 679–684.
56. Masson M. Bromelain in blunt injuries of the locomotor system. A study of observed applications in general practice. Fortschr. Med. 1995; 113: 303–306.
57. Cirelli MG, Smyth RD. Effects of bromelain anti-edema therapy on coagulation, bleeding, and prothrombin times. J. New Drugs. 1963; 3: 37–39.