



Study name

1. Witte MB. and Barbul A.: General principles of wound healing. *Surg Clin North Am* 1997; 77:509.[PubMed]
2. Wischemeyer PE., Kahana M., Wolfson R., Ren H., Musch MM., and Chang EB.: Glutamine induces heat shock protein and protects against endotoxin shock in the rat. *J Appl Physiol* 2001; 90:2403.[PubMed]
3. Wischemeyer PE.: Glutamine and heat shock protein expression. *Nutrition* 2002; 18:225. [PubMed]
4. Aquino VM., Harvey AR., Garvin JH., Godder KT., Nieder ML., Adams RH., Jackson GB., and Sandler ES.: A double-blind randomized placebo-controlled study of oral glutamine in the prevention of mucositis in children undergoing hematopoietic stem cell transplantation: a pediatric blood and marrow transplant consortium study. *Bone Marrow Transplant* 2005; 36:611. [PubMed]
5. Ward E., Smith M., Henderson M., Reid U., Lewis I., Kinsey S., Allgar V., Bowers D., and Picton SV.: The effect of high-dose enteral glutamine on the incidence and severity of mucositis in paediatric oncology patients. *Eur J Clin Nutr* 2009; 63:134. [PubMed]
6. Barbul A., Lazarou S., Efron DT., Wasserkrug HL., and Efron G.: Arginine enhances wound healing in humans. *Surgery* 1990; 108:331. [PubMed]
7. Barbul A., Sisto DA., Wasserkrug HL., Yoshimura NN., and Efron G.: Metabolic and immune effects of arginine in post-injury hyperalimentation. *J Trauma* 1981; 21:970. [PubMed]
8. Debats IB., Wolfs TG., Gotoh T., Cleutjens JP., Peutz-Kootstra CJ., and Van der Hulst RR.: Role of arginine in superficial wound healing in man. *Nitric Oxide* 2009; 21:175. [PubMed]
9. Kirk SJ., Hurson M., Regan MC., Holt DR., Wasserkrug HL., and Barbul A.: Arginine stimulates wound healing and immune function in elderly human beings. *Surgery* 1993; 114:155. [PubMed]
10. Singh K., Coburn LA., Barry DP., Boucher J., Chaturvedi R., and Wilson KT.: L-arginine uptake by cationic amino acid transporter 2 is essential for colonic epithelial cell restitution. *Am J Physiol Gastrointest Liver Physiol* 2012; 302:G1061. [PMC free article][PubMed]
11. Leigh B., Desneves K., Rafferty J., Pearce L., King S., Woodward MC., Brown D., Martin R., and Crowe TC.: The effect of different doses of an arginine-containing supplement on the healing of pressure ulcers. *J Wound Care* 2012; 21:150. [PubMed]
12. Schäffer MR., Tantry U., Thornton FJ., and Barbul A.: Inhibition of nitric oxide synthesis in wounds: pharmacology and effect on accumulation of collagen in wounds in mice. *Eur J Surg* 1999; 165:262. [PubMed]
13. Ueno C., Fukatsu K., Maeshima Y., Moriya T., Omata J., Saitoh D., and Mochizuki H.: Arginine-enriched total parenteral nutrition improves survival in peritonitis by normalizing NFkappaB activation in peritoneal resident and exudative leukocytes. *Ann Surg* 2010; 251:959. [PubMed]
14. Alexander JW.: Immunonutrition: the role of omega-3 fatty acids. *Nutrition* 1998; 14:627.[PubMed]
15. Novak TE., Babcock TA., Jho DH., Helton WS., and Espat NJ.: NF-kappa B inhibition by omega-3 fatty acids modulates LPS-stimulated macrophage TNF-alpha transcription. *Am J Physiol Lung Cell Mol Physiol* 2003; 284:L84. [PubMed]

16. McDaniel JC., Belury M., Ahijevych K., and Blakely W.: Omega-3 fatty acids effect on wound healing. *Wound Rep Reg* 2008; 16:337 [PMC free article] [PubMed]

17. McDaniel JC., Massey K., and Nicolaou A.: Fish oil supplementation alters levels of lipid mediators of inflammation in microenvironment of acute human wounds. *Wound Rep Reg* 2011; 19:189 [PMC free article] [PubMed]

18. Theilla M., Schwartz B., Cohen J., Shaprio H., Anbar R., and Singer P.: Impact of a nutritional formula enriched in fish oil and micronutrients on pressure ulcers in critical care patients. *Am J Crit Care* 2012; 21:102 [PubMed]

19. Albina JE., Gladden P., and Walsh WR.: Detrimental effects of an omega-3 fatty acid-enriched diet on wound healing. *JPEN* 1993; 17:519 [PubMed]

20. Jagetia GC., Rajanikant GK., and Mallikarjun Rao KVN.: Ascorbic acid increases healing of excision wounds of mice whole body exposed to different doses of γ -radiation. *Burns* 2007; 33:484.[PubMed]

21. Taylor TV., Rimmer S., Day B., Butcher J., and Dymock IW.: Ascorbic acid supplementation in the treatment of pressure-sores. *Lancet* 1974; 2:544. [PubMed]

22. Levenson SM., Gruber CA., Rettura G., Gruber DK., Demetriou AA., and Seifter E.: Supplemental vitamin A prevents the acute radiation-induced defect in wound healing. *Ann Surg* 1984; 200:494. [PMC free article] [PubMed]

23. Hunt TK., Ehrlich HP., Garcia JA., and Dunphy JE.: Effect of vitamin A on reversing the inhibitory effect of cortisone on healing of open wounds in animals and man. *Ann Surg* 1969; 170:633. [PMC free article] [PubMed]

24. Berger MM., Baines M., Raffoul W., Benathan M., Chiolero RL., Reeves C., Revely JP., Cayeux MC., S n chaud I., and Shenkin A.: Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations. *Am J Clin Nutr* 2007; 85:1293. [PubMed]

25. Mu oz M., Romero A., Morales M., Campos A., Garcia-Erce JA., and Ramirez G.: Iron metabolism, inflammation and anemia in critically ill patients. A cross-sectional study. *Nutr Hosp* 2005; 20:115 [PubMed]

26. Barbosa E., Faintuch J., Machado Moreira EA., Goncalves da Silva VR., Lopes Pereima MJ., Martins Fagundes RL., and Filho DW.: Supplementation of vitamin E, vitamin C, and zinc attenuates oxidative stress in burned children: a randomized, double-blind, placebo-controlled pilot study. *J Burn Care Res* 2009; 30:859. [PubMed]

27. Wilkinson EA.: Oral zinc for arterial and venous leg ulcers. *Cochrane Database Syst Rev* 2012; 8:CD001273. [PubMed]

28. Blass SC., Goose H., Tolba RH., Stoffel-Wagner B., Kabir K., Burger C., Stehle P., and Ellinger S.: Time to wound closure in trauma patients with disorders in wound healing is shortened by supplements containing antioxidant micronutrients and glutamine: a PRCT. *Clin Nutr* 2012; 31:469. [PubMed]

29. Marik PE. and Zaloga GP.: Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. *JPEN J Parenter Enteral Nutr* 2010; 34:378. [PubMed]

30. Heys SD., Walker LG., Smith I., and Eremin O.: Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg* 1999; 229:467. [PMC free article] [PubMed]

31. Heyland DK., Novak F., Drover JW., Jain M., Su X., and Suchner U.: Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA* 2001; 286:944.[PubMed]

32. Ferreras N., Artigas V., Cardona D., Rius X., Trias M., and González JA.: Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. *Clin Nutr* 2005; 24:55. [PubMed]

33. McCowen KC. and Bistrain BR.: Immunonutrition: problematic or problem solving? *Am J Clin Nutr* 2003; 77:764. [PubMed]

34. raga M., Gianotti L., Nespoli L., Radaelli G., and Di Carlo V.: Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg* 2002; 137:174. [PubMed]

35. Giger U., Büchler M., Farhadi J., Berger D., Hüsler J., Schneider H., Krähenbühl S., and Krähenbühl L.: Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery—a randomized controlled pilot study. *Ann Surg Oncol* 2007; 14:2798. [PubMed]

36. Braga M. and Gianotti L.: Preoperative immunonutrition: cost-benefit analysis. *JPEN* 2005; 29:S57[PubMed]

37. Beale RJ., Sherry T., Lei K., Campbell-Stephen L., McCook J., Smith J., Venetz W., Altelheld B., Stehle P., and Schneider H.: Early enteral supplementation with key pharmacnutrients improves sequential organ failure assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. *Crit Care Med* 2008; 36:131. [PubMed]

38. Heyland DK., Dhaliwal R., Day AG., Muscedere J., Drover J., Suchner U., Cook D., and Canadian Critical Care Trials Group: Reducing deaths due to oxidative stress (The REDOX Study): rationale and study design for a randomized trial of glutamine and antioxidant supplementation in critically-ill patients. *Proc Nutr Soc* 2006; 65:250. [PubMed]

39. Al Balushi RM., Paratz JD., Cohen J., Banks M., Dulhunty J., Roberts JA., and Lipman J.: Effect of intravenous glutamine supplementation in trauma patients receiving enteral nutrition study protocol (GLINT Study): a prospective, blinded, randomised, placebo-controlled clinical trial. *BMJ Open* 2011; 1:2011 [PMC free article] [PubMed]

40. Jones NE. and Heyland DK.: Pharmacnutrition: a new emerging paradigm. *Curr Opin Gastroenterol* 2008; 24:215. [PubMed]

41. Comparative bioavailability to humans of ascorbic acid alone or in a citrus extractJ A Vinson andP Bose;; Chemistry and pharmacology of the citrus bioflavonoid hesperidin A. Garg;; S. Garg;; L. J. D. Zaneveld, A. K. Singla

42. Mondal S, Bhattacharya S, Pandey JN, Biswas M. Evaluation of acute anti-inflammatory effect of Ananas Comosus leaf extract in Rats. *Pharmacologyonline*. 2011;3:1312–1315.

43. Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application: an update. *Journal of Ethnopharmacology*. 1988;22(2):191–203. [PubMed]

44. Heinicke RM, Gortner WA. Stem bromelain: a new protease preparation from pineapple plants. *Economic Botany*. 1957;11(3):225–234.

45. Livio M, Gaetano GDe, Donati MB. Effect of bromelain on fibrinogen level, protrombin complex and platelet aggregation in the rat—a preliminary report. *Drugs under Experimental and Clinical Research*. 1978;1:49–53.

46. Neubauer RA. A plant protease for potentiation of and possible replacement of antibiotics. *Experimental Medicine and Surgery*. 1961;19:143–160. [PubMed]

47. Renzini G, Varego M. Die resorption von tetrazyklin ingenenwart von Bromelain bei oraler application. *Arzneimittel-Forschung Drug Research*. 1972;2:410–412. [PubMed]

48. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cellular and Molecular Life Sciences*. 2001;58(9):1234–1245. [PubMed]

49. Tochi BN, Wang Z, Xu SY, Zhang W. Therapeutic application of pineapple protease (Bromelain): a review. *Pakistan Journal of Nutrition*. 2008;7(4):513–520.

50. Taussig SJ. The mechanism of the physiological action of bromelain. *Medical Hypotheses*. 1980;6(1):99–104. [PubMed]

51. Hale LP. Proteolytic activity and immunogenicity of oral bromelain within the gastrointestinal tract of mice. *International Immunopharmacology*. 2004;4(2):255–264. [PubMed]

52. Ley CM, Tsiami A, Ni Q, Robinson N. A review of the use of bromelain in cardiovascular diseases. *Journal of Chinese Integrative Medicine*. 2011;9(7):702–710. [PubMed]

53. Chobotova K, Vernallis AB, Majid FAA. Bromelain's activity and potential as an anti-cancer agent: current evidence and perspectives. *Cancer Letters*. 2010;290(2):148–156. [PubMed]

54. Castell JV, Friedrich G, Kuhn CS, Poppe GE. Intestinal absorption of undegraded proteins in men: presence of bromelain in plasma after oral intake. *American Journal of Physiology*. 1997;273(1):G139–G146. [PubMed]

55. Bhattacharyya BK. Bromelain: an overview. *Natural Product Radiance*. 2008;7(4):359–363.

56. Rowan AD, Buttle DJ. Pineapple cysteine endopeptidases. *Methods in Enzymology*. 1994;244:555–568.[PubMed]

57. Yoshioka K Izutsa S, Asa Y, Takeda Y. Inactivation kinetics of enzyme pharmaceuticals in aqueous solutions. *Pharmaceutical Research*. 1991;4:480–485. [PubMed]

58. 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(1):41–52.[PubMed]

59. Napper AD, Bennet SP, Borowski M, et al. Purification and characterization of multiple forms of the pineapple-stem-derived cysteine proteinases ananain and comosain. *Biochemical Journal*. 1994;301(3):727–735. [PMC free article] [PubMed]

60. Cooreman W. Bromelain. In: Ruysen R, Lauwers A, editors. *Pharmaceutical Enzymes- Properties and Assay Methods*. Gent, Belgium: E. Story-Scientia Scientific Publishing Co.; 1978. pp. 107–121.

61. Filippova IY, Lysogorskaya EN, Oksenoit ES, Rudenskaya GN, Stepanov VM. L-Pyroglutamyl-L-phenylalanyl-L-leucine-p nitroanilide: a chromogenic substrate for thiol proteinase assay. *Analytical Biochemistry*. 1984;143(2):293–297. [PubMed]

62. Seifert J, Ganser R, Brendel W. Absorption of a proteolytic enzyme originating from plants out of the gastro-intestinal tract into blood and lymph of rats. *Zeitschrift fur Gastroenterologie*. 1979;17(1):1–8.[PubMed]

63. Shiew PS, Fang YL, Majid FAA. In vitro study of bromelain activity in artificial stomach juice and blood. *Proceedings of the 3rd International Conference on Biotechnology for the Wellness Industry; 2010; PWTC;*

64. Neumayer C, Fügler A, Nanobashvili J, et al. Combined enzymatic and antioxidative treatment reduces ischemia-reperfusion injury in rabbit skeletal muscle. *Journal of Surgical Research*. 2006;133(2):150–158.[PubMed]

65. Heinicke RM, van der Wal L, Yokoyama M. Effect of bromelain (Ananase) on human platelet aggregation. *Experientia*. 1972;28(10):844–845. [PubMed]

66. 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(1):41–52.[PubMed]

67. King DE, Ellis TM, Everett CJ, Mainous AG. Medication use for diabetes, hypertension, and hypercholesterolemia from 1988–1994 to 2001–2006. *Southern Medical Journal*. 2009;102(11):1127–1132.[PubMed]

68. Secor ER, Jr., William FC, Michelle MC, et al. Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murin model of allergic disease. *Cellular Immunology*. 2005;237:68–75.[PMC free article] [PubMed]

69. Juhasz B, Thirunavukkarasu M, Pant R, et al. Bromelain induces cardioprotection against ischemia-reperfusion injury through Akt/FOXO pathway in rat myocardium. *American Journal of Physiology*. 2008;294(3):H1365–H1370. [PMC free article] [PubMed]

70. Lawrence RC, Helmich CG, Arnett F, et al. Estimates of prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis & Rheumatism*. 1998;41:778–799. [PubMed]

71. Akhtar NM, Naseer R, Farooqi AZ, Aziz W, Nazir M. Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee—a double-blind prospective randomized study. *Clinical Rheumatology*. 2004;23(5):410–415. [PubMed]

72. Brien S, Lewith G, Walker A, Hicks SM, Middleton D. Bromelain as a treatment for osteoarthritis: a review of clinical studies. *Evidence-Based Complementary and Alternative Medicine*. 2004;1(3):251–257.[PMC free article] [PubMed]

73. Mojcić CF, Shevach EM. Adhesion molecules: a rheumatologic perspective. *Arthritis and Rheumatism*. 1997;40(6):991–1004. [PubMed]

74. Bodi T. The effects of oral bromelains on tissue permeability to antibiotics and pain response to bradykinin: double blind studies on human subjects. *Clinical Medicine*. 1966;73:61–65.

75. Kumakura S, Yamashita M, Tsurufuji S. Effect of bromelain on kaolin-induced inflammation in rats. *European Journal of Pharmacology*. 1988;150(3):295–301. [PubMed]

76. Cohen A, Goldman J. Bromelain therapy in rheumatoid arthritis. *Pennsylvania Medical Journal*. 1964;67:27–30. [PubMed]

77. Barth H, Guseo A, Klein R. In vitro study on the immunological effect of bromelain and trypsin on mononuclear cells from humans. *European Journal of Medical Research*. 2005;10(8):325–331. [PubMed]

78. Hale LP, Haynes BF. Bromelain treatment of human T cells removes CD44, CD45RA, E2/MIC2, CD6, CD7, CD8, and Leu 8/LAM1 surface molecules and markedly enhances CD2-mediated T cell activation. *Journal of Immunology*. 1992;149(12):3809–3816. [PubMed]

79. Lehmann PV. Immunomodulation by proteolytic enzymes. *Nephrology Dialysis Transplantation*. 1996;11(6):953–955. [PubMed]

80. Desser L, Rehberger A, Kokron E, Paukovits W. Cytokine synthesis in human peripheral blood mononuclear cells after oral administration of polyezyme preparations. *Oncology*. 1993;50(6):403–407.[PubMed]

81. Desser L, Rehberger A, Paukovits W. Proteolytic enzymes and amylase induce cytokine production in human peripheral blood mononuclear cells in vitro. *Cancer Biotherapy*. 1994;9(3):253–263. [PubMed]

82. Eckert K, Grabowska E, Stange R, Schneider U, Eschmann K, Maurer HR. Effects of oral bromelain administration on the impaired immunocytotoxicity of mononuclear cells from mammary tumor patients. *Oncology Reports*. 1999;6(6):1191–1199. [PubMed]

83. Engwerda CR, Andrew D, Murphy M, Mynott TL. Bromelain activates murine macrophages and natural killer cells in vitro. *Cellular Immunology*. 2001;210(1):5–10. [PubMed]

84. Engwerda CR, Andrew D, Ladhams A, Mynott TL. Bromelain modulates T cell and B cell immune responses in vitro and in vivo. *Cellular Immunology*. 2001;210(1):66–75. [PubMed]

85. Mynott TL, Ladhams A, Scarmato P, Engwerda CR. Bromelain, from pineapple stems, proteolytically blocks activation of extracellular regulated kinase-2 in T cells. *Journal of Immunology*. 1999;163(5):2568–2575. [PubMed]

86. Secor ER, Jr., Singh A, Guernsey LA, et al. Bromelain treatment reduces CD25 expression on activated CD4+ T cells in vitro. *International Immunopharmacology*. 2009;9(3):340–346. [PMC free article][PubMed]

87. Leipner J, Iten F, Saller R. Therapy with proteolytic enzymes in rheumatic disorders. *BioDrugs*. 2002;15(12):779–789. [PubMed]

88. Lotz-Winter H. On the pharmacology of bromelain: an update with special regard to animal studies on dose-dependent effects. *Planta Medica*. 1990;56(3):249–253. [PubMed]

89. Barth H, Guseo A, Klein R. In vitro study on the immunological effect of bromelain and trypsin on mononuclear cells from humans. *European Journal of Medical Research*. 2005;10(8):325–331. [PubMed]

90. Livio M, De Gaetano G, Donati MB. Effect of bromelain on fibrinogen level, prothrombin complex factors and platelet aggregation in rat: a preliminary report. *Drugs under Experimental and Clinical Research*. 1978;4:21–23.

91. De-Guili M, Pirotta F. Bromelain: interaction with some protease inhibitors and rabbit specific antiserum. *Drugs under Experimental and Clinical Research*. 1978;4:21–23.

92. Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application: an update. *Journal of Ethnopharmacology*. 1988;22(2):191–203. [PubMed]

93. Mynott TL, Guandalini S, Raimondi F, Fasano A. Bromelain prevents secretion caused by *Vibrio cholerae* and *Escherichia coli* enterotoxins in rabbit ileum in vitro. *Gastroenterology*. 1997;113(1):175–184.[PubMed]

94. Chandler DS, Mynott TL. Bromelain protects piglets from diarrhoea caused by oral challenge with K88 positive enterotoxigenic *Escherichia coli*. *Gut*. 1998;43(2):196–202. [PMC free article] [PubMed]

95. Mynott TL, Luke RKJ, Chandler DS. Oral administration of pro tease inhibits enterotoxigenic *Escherichia coli* receptor activity in piglet small intestine. *Gut*. 1996;38(1):28–32. [PMC free article][PubMed]

96. Béez R, Lopes MTP, Salas CE, Hernández M. In vivo antitumoral activity of stem pineapple (*Ananas comosus*) bromelain. *Planta Medica*. 2007;73(13):1377–1383. [PubMed]

97. Taussig SJ, Szekeczes J, Batkin S. Inhibition of tumour growth in vitro by bromelain, an extract of the pineapple plant (*Ananas comosus*) *Planta Medica*. 1985;6:538–539. [PubMed]

98. Tysnes BB, Maurer HR, Porwol T, Probst B, Bjerkvig R, Hoover F. Bromelain reversibly inhibits invasive properties of glioma cells. *Neoplasia*. 2001;3(6):469–479. [PMC free article] [PubMed]

99. Lehmann PV. Immunomodulation by proteolytic enzymes. *Nephrology Dialysis Transplantation*. 1996;11(6):953–955. [PubMed]

100. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436–444. [PubMed]

101. Desser L, Rehberger A, Paukovits W. Proteolytic enzymes and amylase induce cytokine production in human peripheral blood mononuclear cells in vitro. *Cancer Biotherapy*. 1994;9(3):253–263. [PubMed]

102. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. *International Journal of Cancer*. 2007;121(11):2373–2380. [PubMed]

103. 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 Letters*. 2009;282(2):167–176. [PubMed]

104. Huang JR, Wu CC, Hou RCW, Jeng KC. Bromelain inhibits lipopolysaccharide-induced cytokine production in human THP-1 monocytes via the removal of CD14. *Immunological Investigations*. 2008;37(4):263–277. [PubMed]

105. Ferris RL, Grandis JR. NF-κB gene signatures and p53 mutations in head and neck squamous cell carcinoma. *Clinical Cancer Research*. 2007;13(19):5663–5664. [PubMed]

106. Hou RCW, Chen YS, Huang JR, Jeng KCG. Cross-linked bromelain inhibits lipopolysaccharide-induced cytokine production involving cellular signaling suppression in rats. *Journal of Agricultural and Food Chemistry*. 2006;54(6):2193–2198. [PubMed]

107. Wang MT, Honn KV, Nie D. Cyclooxygenases, prostanoids, and tumor progression. *Cancer and Metastasis Reviews*. 2007;26(3-4):525–534. [PubMed]

108. Tassman GC, Zafran JN, Zayon GM. Evaluation of a plate proteolytic enzyme for the control of inflammation and pain. *Journal of Dental Medicine*. 1964;19:73–77.

109. Tassman GC, Zafran JN, Zayon GM. A double-blind crossover study of a plant proteolytic enzyme in oral surgery. *The Journal of Dental Medicine*. 1965;20:51–54. [PubMed]

110. Howat RCL, Lewis GD. The effect of bromelain therapy on episiotomy wounds—a double blind controlled clinical trial. *Journal of Obstetrics and Gynaecology of the British Commonwealth*. 1972;79(10):951–953. [PubMed]

111. Houck JC, Chang CM, Klein G. Isolation of an effective debriding agent from the stems of pineapple plants. *International Journal of Tissue Reactions*. 1983;5(2):125–134. [PubMed]

112. Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application: an update. *Journal of Ethnopharmacology*. 1988;22(2):191–203. [PubMed]

113. Rosenberg L, Kriehner Y, Silverstain E, et al. Selectivity of a Bromelain Based Enzymatic Debridement Agent: A Porcine Study. Elsevier; 2012. [PubMed]

114. Singer AJ, McClain SA, Taira BR, Rooney J, Steinhaff N, Rosenberg L. Rapid and selective enzymatic debridement of porcine comb burns with bromelain-derived Debrase: acute-phase preservation of noninjured tissue and zone of stasis. *Journal of Burn Care and Research*. 2010;31(2):304–309. [PubMed]

115. Wu SY, Hu W, Zhang B, Liu S, Wang JM, Wang AM. Bromelain ameliorates the wound microenvironment and improves the healing of firearm wounds. *Journal of Surgical Research*. 2012;176:503–509. [PubMed]

116. Hu W, Wang AM, Wu SY, et al. Debriding effect of bromelain on firearm wounds in pigs. *The Journal of Trauma*. 2011;71(4):966–972. [PubMed]

117. Miller JG, Carruthers HR, Burd DAR. An algorithmic approach to the management of cutaneous burns. *Burns*. 1992;18(3):200–211. [PubMed]

118. Sheridan RL, Tompkins RG, Burke JF. Management of burn wounds with prompt excision and immediate closure. *Journal of Intensive Care Medicine*. 1994;237:68–75. [PubMed]

119. Salisbury RE. In-thermal burns. In: McCarthy JC, editor. *Plastic Surgery*. Vol. 1. 1990. pp. 787–830.

120. Taussig SJ, Yokoyama MM, Chinen A. Bromelain: a proteolytic enzyme and its clinical application: a review. *Hiroshima Journal of Medical Sciences*. 1975;24(2-3):185–193. [PubMed]

121. Moss IN, Frazier CV, Martin GJ. Bromelain -the pharmacology of the enzyme. *Archives of International Pharmacody*. 1963;145:166–189. [PubMed]

122. Albina JE, Abate JA, Mastrofrancesco B. Role of ornithine as a proline precursor in healing wounds. *J Surg Res* 55: 97–102, 1993 [PubMed]

123. Barbul A. Proline precursors to sustain mammalian collagen synthesis. *J Nutr* 138: 2021S–2024S, 2008[PubMed]

124. Chaturvedi R, Asim M, Lewis ND, Algood HM, Cover TL, Kim PY, Wilson KT. L-arginine availability regulates inducible nitric oxide synthase-dependent host defense against *Helicobacter pylori*. *Infect Immun* 75: 4305–4315, 2007 [PMC free article] [PubMed]

125. Lucotti P, Setola E, Monti LD, Galluccio E, Costa S, Sandoli EP, Fermo I, Rabaiotti G, Gatti R, Piatti P. Beneficial effects of a long-term oral L-arginine treatment added to a hypocaloric diet and exercise training program in obese, insulin-resistant type 2 diabetic patients. *Am J Physiol Endocrinol Metab* 291: E906–E912, 2006 [PubMed]

126. J.C.L. Neyens, E. Cereda, E.P. Meijer, C. Lindholm, J.M.G.A. Schols. (2017) Arginine-enriched oral nutritional supplementation in the treatment of pressure ulcers: A literature review. *Wound Medicine* 16, 46-51

127. Emanuele Cereda, J. C. L. Neyens, R. Caccialanza, M. Rondanelli, J. M. G. A. Schols. (2016) Efficacy of a disease-specific nutritional support for pressure ulcer healing: A systematic review and meta-analysis. *The journal of nutrition, health & aging*

128. J. Wesley Alexander, Dorothy M. Supp. (2014) Role of Arginine and Omega-3 Fatty Acids in Wound Healing and Infection. *Advances in Wound Care* 3:11, 682-690

129. Sabine Ellinger. (2014) Micronutrients, Arginine, and Glutamine: Does Supplementation Provide an Efficient Tool for Prevention and Treatment of Different Kinds of Wounds?. *Advances in Wound Care* 3:11, 691-707

130. David R. Thomas. (2014) Role of Nutrition in the Treatment and Prevention of Pressure Ulcers. *Nutrition in Clinical Practice* 29:4, 466-472

131. Seifter E, Crowley LV, Rettura G, Nakao K, Gruber C, Kan D, Levenson SM. Influence of vitamin A on wound healing in rats with femoral fracture. *Ann Surg*. 1975 Jun;181(6):836–841.[PMC free article] [PubMed]

132. Ehrlich HP, Hunt TK. Effects of cortisone and vitamin A on wound healing. *Ann Surg*. 1968 Mar;167(3):324–328. [PMC free article] [PubMed]

133. Peck MD, Chang Y. Nutritional support for burn injuries. *J Nutr Biochem* 1999;10:380–96.

134. Meyer NA, Muller MJ, Herndon DN. Nutrient support of the healing wound. *New Horizons* 1994;2:202–14.

135. Berger MM, Binnert C, Chioloro RL, et al. Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism. *Am J Clin Nutr* 2007;85:1301–6.

136. Jonas J, Burns J, Abel EW, Cresswell MJ, Strain JJ, Paterson CR. Impaired mechanical strength of bone in experimental copper deficiency. *Ann Nutr Metab* 1993;37:245–52.

137. Rucker RB, Kosonen T, Clegg MS, et al. Copper, lysyl oxidase, and extracellular matrix protein cross-linking. *Am J Clin Nutr* 1998;67(suppl):S996–1002.

138. Schwartz JR, Marsh RG, Draelos ZD. Zinc and skin health: overview of physiology and pharmacology. *Dermatol Surg* 2005;31:837–47.

139. Berger MM, Chioloro R. Relations between copper, zinc and selenium intakes and malondialdehyde excretion after major burns.

140. Shenkin A. Micronutrients and antioxidants in home parenteral nutrition. *Clin Nutr* 2001;20(suppl):47–50.

141. Berger MM. Acute copper and zinc deficiency due to exudative losses—substitution versus nutritional requirements. *Burns* 2005;31:711–6.

142. Shenkin A. Trace elements and inflammatory response: implications for nutritional support. *Nutrition* 1995;11:100–5.

143. DiSilvestro, R.A. Zinc in relation to diabetes and oxidative disease. *J Nutr.* 2000;130 (1509S-11S). PubMed

144. Ellinger, S., Stehle, P. Efficacy of vitamin supplementation in situations with wound healing disorders: results from clinical intervention studies. *Curr Opin Clin Nutr Metab Care.* 2009;12:588–595

145. Furst, P., Albers, S., Stehle, P. Evidence for a nutritional need for glutamine in catabolic patients. *Kidney International Suppl.* 1989;27:S287–S292.

146. Wilmore, D.W. The effect of glutamine supplementation in patients following elective surgery and accidental injury. *J Nutr.* 2001;131 (2543S-9S; [discussion 50S-1S]). PubMed

147. Roggenbuck, C., Lammert, F., Berthold, H.K., Giese, T., Stallmach, A., Stehle, P. et al. High-dose oral supplementation of antioxidants and glutamine improves the antioxidant status in patients with Crohn's disease: a pilot study. *e-SPEN, Eur e-Journal Clin Nutr Metab.* 2008;3/5:e246–e253

148. Morrissey, P.A., Sheehy, P.J., Gaynor, P. Vitamin E. *Int J Vitam Nutr Res.* 1993;63:260–264. PubMed

149. Berger MM, Binnert C, Chioloro RL, et al. Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism. *Am J Clin Nutr* 2007;85:1301–6.

150. Jonas J, Burns J, Abel EW, Cresswell MJ, Strain JJ, Paterson CR. Impaired mechanical strength of bone in experimental copper deficiency. *Ann Nutr Metab* 1993;37:245–52.

151. Rucker RB, Kosonen T, Clegg MS, et al. Copper, lysyl oxidase, and extracellular matrix protein cross-linking. *Am J Clin Nutr* 1998;67(suppl):S996–1002.

152. Schwartz JR, Marsh RG, Draelos ZD. Zinc and skin health: overview of physiology and pharmacology. *Dermatol Surg* 2005;31:837–47.

153. Berger MM, Chioloro R. Relations between copper, zinc and selenium intakes and malondialdehyde excretion after major burns.

154. Shenkin A. Micronutrients and antioxidants in home parenteral nutrition. *Clin Nutr* 2001;20(suppl):47–50.

155. Berger MM. Acute copper and zinc deficiency due to exudative losses—substitution versus nutritional requirements. *Burns* 2005;31:711–6.

156. Shenkin A. Trace elements and inflammatory response: implications for nutritional support. *Nutrition* 1995;11:100–5.

157. DiSilvestro, R.A. Zinc in relation to diabetes and oxidative disease. *J Nutr*. 2000;130 (1509S-11S). PubMed

158. Ellinger, S., Stehle, P. Efficacy of vitamin supplementation in situations with wound healing disorders: results from clinical intervention studies. *Curr Opin Clin Nutr Metab Care*. 2009;12:588–595

159. Furst, P., Albers, S., Stehle, P. Evidence for a nutritional need for glutamine in catabolic patients. *Kidney International Suppl*. 1989;27:S287–S292.

160. Wilmore, D.W. The effect of glutamine supplementation in patients following elective surgery and accidental injury. *J Nutr*. 2001;131 (2543S-9S; [discussion 50S-1S]). PubMed

161. Roggenbuck, C., Lammert, F., Berthold, H.K., Giese, T., Stallmach, A., Stehle, P. et al, High-dose oral supplementation of antioxidants and glutamine improves the antioxidant status in patients with Crohn's disease: a pilot study. *e-SPEN, Eur e-Journal Clin Nutr Metab*. 2008;3/5:e246–e253

162. Morrissey, P.A., Sheehy, P.J., Gaynor, P. Vitamin E. *Int J Vitam Nutr Res*. 1993;63:260–264. PubMed

163. Mora RJ, Mora RJ. Malnutrition: organic and functional consequences. *World J Surg.* 1999;23:530-535. [Google Scholar](#) [Medline](#)

164. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med.* 2001;29:2264-2270. [Google Scholar](#) [CrossRef](#), [Medline](#)

165. Zaloga GP, Siddiqui RA. Biologically active dietary peptides. *Mini Rev Med Chem.* 2004;4:815-821. [Google Scholar](#) [Medline](#)

166. Heyland D, Dhaliwal R. Immunonutrition in the critically ill: from old approaches to new paradigms. *Intensive Care Med.* 2005;31:501-503. [Google Scholar](#) [Medline](#)

167. Blass, S.C., Ellinger, S., Goost, H., Engels, J., Wirtz, D.C., Burger, C. et al, Deficiencies in zinc and selenium status are common in elderly trauma patients. *Clin Nutr.* 2007;2:157–158.

168. Popovic PJ, Zeh HJIII, Ochoa JB. Arginine and immunity. *J Nutr.* 2007;137(6 suppl 2):1681S-1686S. [Google Scholar](#) [Medline](#)

169. Horie H, Okada M, Kojima M, Nagai H. Favorable effects of preoperative enteral immunonutrition on a surgical site infection in patients with colorectal cancer without malnutrition. *Surg Today.* 2006;36:1063-1068. [Google Scholar](#) [Medline](#)

170. Giger U, Buchler M, Farhadi J, . Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. *Ann Surg Oncol.* 2007;14:2798-2806. [Google Scholar](#) [Medline](#)

171. Lobo DN, Williams RN, Welch NT, . Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. *Clin Nutr.* 2006;25:716-726. [Google Scholar](#) [Medline](#)

172. Snyderman CH, Kachman K, Molseed L, . Reduced postoperative infections with an immune-enhancing nutritional supplement. *Laryngoscope.* 1999;109:915-921. [Google Scholar](#) [Medline](#)

173. De Luis DA, Aller R, Izaola O, Cuellar L, Terroba MC. Postsurgery enteral nutrition in head and neck cancer patients. *Eur J Clin Nutr.* 2002;56:1126-1129. [Google Scholar](#) [Medline](#)

174. Jiang XH, Li N, Zhu WM, Wu GH, Quan ZW, Li JS. Effects of postoperative immune-enhancing enteral nutrition on the immune system, inflammatory responses, and clinical outcome. *Chin Med J.* 2004;117:835-839. [Google Scholar](#) [Medline](#)

175. Casas-Rodera P, Gomez-Candela C, Benitez S, . Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomized clinical trial. *Nutr Hosp.* 2008;23:105-110. [Google Scholar](#) [Medline](#)

176. Daly JMLieberman MDGoldfine J et al. Enteral nutrition with supplemental arginine, RNA, and ω 3 fatty acids in patients after operation: immunologic, metabolic and clinical outcome. *Surgery.* 1992;11256- 67

177. Vignali ABraga MGianotti LCestari AProfili MDi Carlo V Impact of an enriched enteral formula on immune function and nutritional status in cancer patients following surgery. Riv Ital Nutr Parenter Enter. 1995;1325- 31

178. Braga MVignali AGianotti LCestari AProfili MDi Carlo V Immune and nutritional effects of early enteral nutrition after major abdominal operations. Eur J Surg. 1996;162105- 112

179. Kemen MSenkal MHomann HH et al. Early postoperative enteral nutrition with arginine, ω -3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact®. Crit Care Med. 1995;23652- 659Article

180. Senkal MKemen MHomann HH et al. Modulation of postoperative immune response by enteral nutrition with a diet enriched with arginine, RNA, and ω -3 fatty acids in patients with upper gastrointestinal cancer. Eur J Surg. 1995;161115- 122

181. Cerra FBLehmann SKonstantinides N et al. Improvement in immune function in ICU patients by enteral nutrition supplemented with arginine, RNA, and menhaden oil is independent of nitrogen balance. Nutrition. 1991;7193- 199

182. Daly JMWeintraub FNShou JRosato EFLucia M Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. Ann Surg. 1995;221327- 338Article

183. Bower RHCerra FBBershadsky B et al. Early enteral administration of a formula (Impact®) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit Care Med. 1995;23436- 449Article

184. Gottschlich MMJenkins MWarden GD et al. Differential effects of three dietary regimens on selected outcome variables in burn patients. JPEN J Parenter Enteral Nutr. 1990;14225- 236Article

185. Braga MVignali AGianotti LCestari AProfili MDi Carlo V Benefits of early postoperative enteral feeding in cancer patients. Infusionther Transfusionmed. 1995;22280- 284

186. Gianotti LBraga MVignali A et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasm. Arch Surg. 1997;1321222- 1230Article

187. Braga MGianotti LVignali ACestari ABisagni PDi Carlo V Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. Crit Care Med. 1998;2624- 30Article

188. Heslin MJLatkany LLeung D et al. A prospective randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg. 1997;226567- 580Article

189. Senkal MMumme AEickhoff U et al. Early postoperative immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. Crit Care Med. 1997;251489- 1496Article

190. Moore FAMoore EEKudsk KA et al. Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. J Trauma. 1994;37607- 615Article

191. Kemen MSenkall MHomann HH et al. Early postoperative enteral nutrition with arginine, ω -3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact®. *Crit Care Med.* 1995;23:652- 659Article

192. Kudsk KAMinard GCroce MA et al. A randomized trial of isonitrogenous enteral diets after severe trauma. *Ann Surg.* 1996;224:531- 543Article

193. Saffle JRWiebke GJennings KMorris EBarton RG Randomized trial of immuno-enhancing enteral nutrition in burn patients. *J Trauma.* 1997;42:793- 802Article

194. Mendez CJurkovich GJGarcia I et al. Effects of immuno-enhancing diet in critically injured patients. *J Trauma.* 1997;42:933- 941Article

195. Braga MGianotti LCestari A et al. Gut function, immune and inflammatory responses in patients perioperatively fed with supplemented formulas. *Arch Surg.* 1996;131:1257- 1265

196. Tepaske R, Velthuis H, Oudemans-van Straaten HM, . Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial. *Lancet.* 2001;358:696-701. Google Scholar Medline

197. Braga M, Gianotti L, Nespoli L, Radaelli G, Di C. Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg.* 2002;137:174-180. Google Scholar Medline

198. Helminen H, Raitanen M, Kellosalo J. Immunonutrition in elective gastrointestinal surgery patients. *Scand J Surg.* 2007;96:46-50. Google Scholar Abstract

199. Braga MGianotti LVignali ACestari ABisagni PDi Carlo V Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. *Crit Care Med.* 1998;26:24- 30Article

200. Witte MB, Barbul A. Arginine physiology and its implication for wound healing. *Wound Repair Regen.* 2003;11:419-423. Google Scholar Medline

201. Moore FA, Moore EE, Kudsk KA, . Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. *J Trauma.* 1994;37:607-615. Google Scholar Medline

202. Cerra FB, Lehman S, Konstantinides N, Konstantinides F, Shronts EP, Holman R. Effect of enteral nutrient on in vitro tests of immune function in ICU patients: a preliminary report. *Nutrition.* 1990;6:84-87. Google Scholar Medline

203. Daly JM, Reynolds J, Thom A, . Immune and metabolic effects of arginine in the surgical patient. *Ann Surg.* 1988;208:512-523. Google Scholar Medline

204. Boger RH, Bode-Boger SM. The clinical pharmacology of L-arginine. *Ann Rev Pharmacol Toxicol.* 2001;41:79-99. Google Scholar Medline

205. Wortel CH, van Deventer SJ, Aarden LA, . Interleukin-6 mediates host defense responses induced by abdominal surgery. *Surgery.* 1993;114:564-570. Google Scholar Medline

206. Roumen RM, Hendriks T, van der Ven-Jongekrijg, J, . Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma: relation with subsequent adult respiratory distress syndrome and multiple organ failure. *Ann Surg.* 1993;218:769-776. Google Scholar Medline

207. Palombo JD, Demichele SJ, Boyce PJ, . Effect of short-term enteral feeding with eicosapentaenoic and gamma-linolenic acids on alveolar macrophage eicosanoid synthesis and bactericidal function in rats. *Crit Care Med.* 1999;27:1908-1915. Google Scholar Medline

208. Mancuso P, Whelan J, Demichele SJ, Snider CC, Guszczka JA, Karlstad MD. Dietary fish oil and fish and borage oil suppress intrapulmonary proinflammatory eicosanoid biosynthesis and attenuate pulmonary neutrophil accumulation in endotoxic rats. *Crit Care Med.* 1997;25:1198-1206. Google Scholar Medline

209. Mancuso P, Whelan J, Demichele SJ, . Effects of eicosapentaenoic and gamma-linolenic acid on lung permeability and alveolar macrophage eicosanoid synthesis in endotoxic rats. *Crit Care Med.* 1997;25:523-532. Google Scholar Medline

210. Ariel A, Serhan CN. Resolvins and protectins in the termination program of acute inflammation. *Trends Immunol.* 2007;28:176-183. Google Scholar Medline

211. Serhan CN. Resolution phase of inflammation: novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. *Ann Rev Immunol.* 2007;25:101-137. Google Scholar Medline

212. Boger RH, Bode-Boger SM. The clinical pharmacology of L-arginine. *Ann Rev Pharmacol Toxicol.* 2001;41:79-99. Google Scholar Medline

213. Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. *Guy's Hospital Intensive Care Group. Crit Care Med.* 1998;26:1164-1172. Google Scholar Medline

214. Gadek JE, Demichele SJ, Karlstad MD, . Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. *Enteral Nutrition in ARDS Study Group. Crit Care Med.* 1999;27:1409-1420. Google Scholar Medline

215. Gianotti L, Braga M, Fortis C, . A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. *JPEN J Parenter Enteral Nutr.* 1999;23:314-320. Google Scholar Abstract

216. Wilkinson EA. and Hawke CI.: Does oral zinc aid the healing of chronic leg ulcers? A systematic literature review. *Arch Dermatol* 1998; 134:1556. [PubMed]

217. Peterson JM., Barbul A., Breslin RJ., Wasserkrug HL., and Efron G.: Significance of T-lymphocytes in wound healing. *Surgery* 1987; 102:300. [PubMed]

218. Efron JE., Frankel HL., Lazarou SA., Wasserkrug HL., and Barbul A.: Wound healing and T-lymphocytes. *J Surg Res* 1990; 48:460. [PubMed]