# 牛初乳蛋白水解物在體外之免疫調節及細胞活性之研究


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**摘 要**

牛初乳為母牛於產犢後數天之內所分泌之乳汁。初乳不僅含有常乳之營養成分，尚含常乳所沒有或含量相當低之生長、抗菌和免疫調節因子。許多研究發現牛初乳可提升新生動物感染細菌的抵抗能力和抑制細菌毒素之活性及免疫調節活性。 本研究以不同之酵素(alcalase, flavourzyme, porcine intestinal enzymes)進行乳牛分娩後1~5天之脫脂乳、酪蛋白及乳清之水解反應，以探討所得水解物對U937 細胞之生長抑制作用及對於人類周邊血液單核球細胞生長之影響。 研究結果顯示，隨著母牛分娩天數的增加，對U937細胞生長抑制效果有降低的趨勢，其中以脫脂乳(濃度1000 μg/mL時，其抑制率為26.67%)之抑制效果為最佳；且經由酵素水解後之初乳水解物(濃度1000 μg/mL時，其抑制率為56.20%)之抑制效果皆高於未經酵素水解之初乳蛋白。另外亦發現，脫脂牛初乳及其水解物經由間接抑制模式，不但能抑制U937細胞之生長，並能誘導其分化為正常人類單核球或巨噬細胞。而脫脂牛初乳及其水解物皆具有促進人類單核細胞生長之能力，且亦能有效有提升T細胞、Tc細胞、B細胞、Th細胞及自然殺手細胞之比率。此外，由脫脂牛初乳及其水解物與單核細胞共同培養之條件培養液中，也測得具有免疫調節作用之細胞激素IL-1 β、TNF- α及IFN- γ。



關鍵詞 : 牛初乳、初乳蛋白水解物、豬小腸粗酵素、白血病細胞U937、免疫調節活性、細胞激素


**目錄**

## 參考文獻

1.江淑華。2005。牛初乳及其酵素水解物之抗氧化性與其蛋白質組成之相關性研究。私立大葉大學生物產業科技學系博士論文，彰化。 2.行政院衛生署。2010。99年死因統計表。 3.林玫欣。1999。鯖魚肉與內臟水解物之抗氧化性研究。國立台灣海洋大學食品科學系碩士論文，基隆。 4.吳則雄。1980。認識牛的初乳。乳業。98/99: 9-14。 5.許清祥。2004。免疫學。合記圖書出版社。 6.原田淳、西村信明。1995。酵素分解調味料的特殊用途，食品加工包裝技術。34 (11): 35-38。 7.宮華婷。2006。初乳之免疫調節作用及對人類白血病細胞(U937)之抑制效果。國立台灣大學食品科技研究所碩士論文，台北。 8.徐麗嵐。2002。以柳松菇與鴻喜菇誘導人類白血病細胞（U937）分化及對Balb/c 鼠皮下移植CT26 腫瘤之抑制效果。國立台灣大學食品科技研究所碩士論文。台北，台灣。 9.歐馨婷。2001。多種蔬菜抑制人類白血病細胞（U937）增殖與誘導其分化之探討。國立台灣大學食品科技研究所碩士論文。台北，台灣。 10.陳昭誠、杜艷櫻、張鴻民。1999。牛乳IgG之酵素水解物性質。食品科學。 11.郭智宏。2001。腸道吸收-胺基酸與胜?。食品工業，33 (5):15-25 12.楊詠翔。1999。食品中抗高血壓胜?的發展現況。食品工業。31: 9-18。 13.楊正護。1983。剩餘初乳利用性之研究。國立中興大學畜牧研究所碩

士論文，台中。 14.鄭名凡。1999。蛋白質水解物的功能與應用。食品資訊。160: 49-54。 15.蘇家愷。1995。自牛初乳中分離免疫球蛋白與乳鐵蛋白。國立台灣大學食品科技研究所博士論文，台北。 16.盧健宇、陳全木、林慶文。2003。乳鐵蛋白素之抗菌表現及其 應用。食品工業。35: 61-65。 17.AOAC.1995. Offical method of Analysis, 14th ed. Association of Offical Analytical Chemists, Washington, D.C., U.S.A. 18.Al-Mashikhi, S. A. and Nakai, S. 1987. Isolation of bovine immuneoglobulins and lactoferin from whey protein by gel filtrateion techniques. J. Dairy Sci. 70: 2486-2492. 19.Alluwaimi. A. M. 2004. The cytokines of bovine mammary gland: prospects for diagnosis and therapy. Res. Vet. Sci. 77: 211-222. 20.Baveye, S., Elass, E., Mazurier, J., Spik, G. and Legrand, D. 1999. Lactoferrin: a multifunctional glycoprotein involved in the modulation of the inflammatory process. Clin. Chem. Lab. Med. 37(3): 281-286. 21.Beutler, B. 2004. Innate immunity: an overview. Mol. Immunol. 40: 845 – 59. 22.Besser, T.E. and Gay, C.C. 1994. The importance of colostrum to the health of the neonatal calf. Veterinary Clin North Amer Food Anim Practice ;10:107 – 17. 23.Blum, J.W. and Hammon, H., 2000. Colostrum effects on the gastrointestinal tract, and on nutritional, endocrine and metabolic parameters in neonatal calves. Livestock Production Science 66: 151 – 159 24.Blum, J.W. and Hammon, H., 1999b. Pancreatic hormones (insulin and glucagon) in calves: ontogenetic changes and nutritional effects. In: Pierzynowski, S.G., Zabielski, R. (Eds.), Biology of the Pancreas in Growing Animals. Elsevier, Amsterdam, pp. 27 – 44. 25.Bogdan, C. 2000. The function of nitric oxide in the immune system. in Handbook of Experimental Pharmacology.volume: Nitric Oxide (ed. Mayer, B.). p. 443 – 492. 26.Brody, E.P. 2000. Biological activities of bovine glycomacropeptide. Br J Nutr. 84 (Suppl 1) : 39-46. 27.Brun, J. M. and Dalgleish, D. G. 1999. Some effects of heart on the competitive adsorption of casein and whey proteins in oil-in water emulsions. Int. Daily J. 9: 323-327 28.Brunner, J. R. 1981. Cow milk proteins: Twenty-five years of progress. J. Dairy Sci. 64: 1038-1054. 29.Campana, W.M. and Baumrucker, C.R., 1995. Hormones and growth factors in bovine milk. In: Jensen, R.G. (Ed.), Handbook of Milk Composition. Academic Press, New York, pp. 476 – 494. 30.Carswell, E., Old, L., Kassel, R., Green, N., Fiore, N. and Williamson, B. 1975. An endotoxin-induced serum factor that causes necrosis of tumors. Proc. Natl. Acad. Sci. U.S.A., 72 (9): 3666-3670. 31.Chakraborty, A. and Basak, S. 2007. pH-induced structural transitions of caseins. Journal of Photochemistry and Photobiology B: Biology 87:191 – 199 32.Chen, H. M., Muramoto, K. and Yamauchi, F. 1995. Structural analysis of antioxidative peptides from soybean β-conglycinin. J. Agric. Food Chem. 43(3): 574-578. 33.Cheung, H. S. and Chushman, D. W. 1971.spectrophotometric assay and properties of the angiotensin-converting enzyme of rabbit lung. Biochem. Pharmacol. 20: 1637-1648. 34.Clement, A. 2000.Enzymatic protein hydrolysates in human nutriation.Trends Food Sci. Technol. 11: 254-262. 35.Clement, A. and Chambers, S. J. 2000. Development and production of hypoallergenic protein hydrolysates for use in infant formulas. Food Allergy Int.1: 175-190. 36.Donnet-Hughes, A., Duc, N., Serrant, P., Vidal, K. and Schiffrin, E.J. 2000. Bioactive molecules in milk and their role in health and disease: the role of transforming growth factor- β . Immunol Cell Biol 78(1): 74-79. 37.Elfstrand, L.Lindmark-Mansson, L., Paulsson, M., Nyberg, L. and Akesson, B. 2002. Immunoglobulins, growth factors and growth hormone in bovine colostrum and the effects of processing. IntDairy J 12(11): 879 – 887. 38.Fagbenro, O. and Tauncery, K. 1993. Chemical and nutriational uality of raw, cooked and salted fish silage. Food Chem. 48: 331-335. 39.Fiat, A-M, Migliore-Samour. D. and Tolles, P. 1993. Biologically ctive peptides from milk proteins with emphasis on two samples concerning antitrombotic and immuneomodulating activeities. J. Daily Sci. 76: 301-310. 40.Fiat, A.M. and Jolles, P. 1989. Caseins of various origins and biologically active casein peptides and oligosaccharides: structural and physiological aspects. Mol Cell Biochem 87(1): 5-30. 41.Frokjaer, S. 1994. Use of hydrolysates for protein supplementation.Food Technol 10: 86-88. 42.Garnier, C., Michon, C., Durand, G. S., Cuvelier, J.L. Doublier, B. Launay, and Colloids, Surf, B. 2003. Biointerfaces 31: 177. 43.Gildberg, A. 1993. Enzymatic processing of marine raw materials. Process Biochem. 28: 1-15. 44.Gildberg, A., Hermes, J. E. and Orejana, F. M. 1984. Acceleration of autolysis during fish sauce fermemtation by adding acid and reducing the salt content. J. Sci. Food Agric. 35: 1363-1369. 45.Gill, H. S. and Cross, M. L. 2000.Anticancer propertyes of bovine milk. Br. J. Nutri. 84: S161-S166. 46.Giri, B., Gomes, A., Debnath, A., Sahaa, A., Biswas, A. K., Dasgupta, S. C. And Gomes, A. 2006. Antiproliferative, cytotoxic and apoptogenic activity of Indian toad (Bufo melanostictus, Schneider) skin extract on U937 and K562 cells. Toxicon 48:388 – 400. 47.Goldman, A.S., Chheda, S. and Garofalo, R., 1997. Spectrum of immunomodulating agents in human milk. Int. J. Ped. Hemat. Onc. 4, 491 – 497. 48.Goldsby, R.A., Kindt, T.J., Osborne, B.A. and Kuby, J. 2003. Immunology. 5 th ed. W. H. Freeman Co., New York. 49.Green, M., Scott, K. J., Anderson, M., Griffin, M. C. and Glover, F. 1984. Chemical characterization of milk concentrated by ultrafiltratio. J. Dairy Res. 51: 267-278. 50.Gurr, M. I. 1981. Review of the progress of dairy science: Human and artificial milks for infant feeding. J. Dairy Res. 48: 519-554. 51.Gru··tter, R., and Blum, J.W., 1991b. Insulin-like growth factor I in neonatal calves fed colostrum or whole milk and injected with growth hormone. J. Anim. Physiol. Anim. Nutr. 66, 231 – 239. 52.Hagiwara, K., Kataoka, S., Yamanaka, H., Kirisawa, R. and Iwai, H. 2000. Detection of cytokines in bovine colostrum. Vet Immunol Immunopathol 76(3-4): 183-190. 53.Hanada, T. and Yoshimura, A. 2002. Regulation of cytokine signaling and inflammation. Cytokine Growth Factor Rev., 13 (4-5): 413- 21. 54.Heine, W.E., Klein, P.D. and Reeds, P.J. 1991. The importance of alpha-lactalbumin in infant nutrition. J Nutr 121(3): 277-283. 55.Hekmat, S. and MaMahon, D. J. 1998. Distribution of iron between caseins and whey proteins in acidified milk.Lebensm.-Wiss. u. – Technol. 31: 632-638. 56.Hooijdonk, A. C. M. van, Kussendrager, K. D. and Strijns, J. M. 2000. In vivo antimicrobial and antiviral activity of components in bovine milk and colostrums involved in non-specific defence. Br. J. Nutri. 84: S127-S134. 57.Hsieh, C. C. 2006. Used rapid phagocytosis screening system to evaluate herbs in anti-inflammation and promote immunity effects. Yearbook of Chinese Medicine and Pharmacy, 24(2): 95-148. 58.Hummel, B. 1959. A modified spectrophotometeric determineation of chymotrypsin, trypsin, and thrombin. Can. J. Biochem Physiol. 371-393. 59.Hurley, W.L., Grieve, R.C,, Magura, C.E., Hegarty, H.M. and Zou, S. 1995. Evidence supporting the mechanism of enteric protection provided by colostral whey fed supplements. Proc Am Assoc Bovine Pract 27: 193-198. 60.Jantova, S., Cipak, L. and Letasiova, S. 2007. Berberine induces apoptosis through a mitochondrial/caspase pathway in human promonocytic U937 cells. Toxicology

in Vitro 21:25 – 31. 61.Jolles, P. and Migliore-Samour, D. 1986. Preparation of immunological agents by treating lipid-free bovine casein with proteolytic enzyme and fractionating the product Patent Assignee: Rhone-Poulenc Sante. United States Patent 4: 851-509, European Patent: 170-550. 62.Jolles, P., Migore-Samour, D. and Parker, F. 1988. Immuno Stimulant substances derived from bovine casein and compositions containing the same. Patent Assignee: Rhone-Poulenc Sante. United States Patent 4: 777-243. 63.Jolles, P. and Migliore-Samour, D. 1986. Preparation of immunological agents by treating lipid-free bovine casein with proteolytic enzyme and fractionating the product. Patent Assignee: Rhone-Poulenc Sante. United States Patent 4 851 509, European Patent 170 550. 64.Kalliomaki, M., Ouwehand, A., Arvilommi, H., Kero, P. and Isoauri, E. 1999. Transforming growth factor- β in breast milk: A potential regulator of atopic disease at an early age. J Allergy Clin Immunol 104(5) 1251-1257. 65.Kayser, H. and Meisel, H. 1996. Stimulation of human peripheral blood lymphocytes by bioactive peptide derived from bovine milk proteins. FEBS Lett.383: 18-20. 66.Koldovsky, O. 1989. Search for a role of milk-borne biologically active peptides for the suckling pig. J. Nutr. 119, 1543 – 1551. 67.Kosikowski, F. V. 1983. Low sodium cheddar cheese through whole milk retentate supplementation. J. Dairy Sci. 66: 2494-2500. 68.Krishnadasan, B., Naidu, B., Byrne, K., Fraga, C., Verrier, E. and Mulligan, M. 2003. The role of proinflammatory cytokines in lung ischemia – reperfusion injury. J. Thorac. Cardiovasc Surg., 125 (2): 261 – 272. 69.Kroening, T.A,, Mukerji, P. and Hards, R.G. 1998. Analysis of beta-casein and its phosphoforms in human milk. Nutr Res 18(12): 1175-1186. 70.Kuhara, T., Iigo, M., Itoh, T., Ushida, Y., Sekine, K., Terada, N., Okamura, H. and Tsuda, H. 2000. Orally administered lactoferrin exerts an antimetastatic effect and enhances production of IL-18 in the intestinal epithelium. Nutr Cancer 38(2): 192-199. 71.Kulkarni, P. R. and Pimpale, N. V. 1989. Colostrum—a review. Indian Journal of Dairy Science, 42, 216 – 224. 72.Kuo, K. P. and Cheryan, M. 1983. Ultrafiltration of acid whey in a spiral wound unit: effect of operating parameters on membrane fouling. J. Food Sci. 48: 1113-1118. 73.Laemmli, U. K. 1970. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature.227, 680-685 74.Lahl, W. J. and Brum, S. T. 1994. Enzymatic production of protein hydrolysates for food use. Food Technol. 48(10): 68-71. 75.Lander, H. M., Sehajpal, P., Levine, D. M. and Novogrodsky, A. 1993. Activation of human peripheral blood mononuclear cells by nitric oxide-generating compound. J. Immunol., 150: 1509-1516. 76.Larson, B. L. 1992. Immunoglobulins of the mammary secretions. In P. F. Fox (Ed.), Advanced dairy chemistry-1: Proteins (pp. 231 – 254). Barking: Elsevier Science Publishers 77.Lazarov, S., Balutsov, M. and Ianev, E. 2000. The role of bacterial endotoxins, receptors and cytokines in the pathogenesis of septic (endotoxin) shock. Vutr. Boles., 32: 33 – 40. 78.Legdeur MC, Bontje PM, Ossenkoppele GJ, Beelen RH, van de Loosdrecht AA, Broekhoven, M.G., Langenhuijsen, M.M., Thijsen, S.F., Hofstee, H. and Schuurhuis, G.J. 1996. The role of BCL-2 and bax protein in monocyte-mediated apoptosis in human leukemic cell lines. Exp Hematol 24(13): 1530-1539. 79.Letterio, J.J., Geiser, A.G., Kulkarni, A.B., Roche, N.S., Sporn, M.B. and Roberts, A.B. 1994. Maternal rescue of transforming growth factor-bata1 null mice. Science 264(5167): 1936-1938. 80.Levay, P.F. and Viljoen, M. 1995. Lactoferrin: a general review. Haematologica. 80(3): 252-267. 81.Liang, C. W., Lai, Y. C. and Chu, Y. H. 2004. A study of the effects on nine Chinese herbs on proinflammatory cytokines production in two cell culture models. J. Chin. Med., 15(4): 293-304. 82.Lieu, C.W., Lee, S.S. and Wang, S.Y. 1992. The effect of Ganoderma lucidum on induction of differentiation in leukemic U937 cells. Anticancer Res 12(4): 1211-1216. 83.Lindmark-Mansson, H. and Akesson, B. 2000. Antioxidative factors in milk. Br. J. Nutri. 84: S103-S110. 84.Lonnerdal, B. and Glazier, C. 1985. Calcium binding by α -lactalbumin in human milk and bovin milk. J Nutr 115(9): 1209-1216. 85.Lotem, J. and Sachs, L. 1987. Regulation of cell-surface receptors for hematopoietic differentiation-inducing protein MGI-2 on normal and leukemic myeloid cells. Int J Cancer 40(4): 532-539. 86.Ma, C.Y., Kung, H. T., Chen, J. N., Chang, C. Y., Chang, H. M. and Wu, S. B. 2009. Effect of bovine colostrum on the growth inhibition and differentiation of human leukemic U937 cells. J. Sci. Food Agric. 89, 965-969. 87.Mackie, I. M. 1982. Fish protein hydrolysates. Process Biochem. 31: 26-31. 88.Mackie, I. M. 1982. Fish protein hydrolysates. Process Biochem. 17: 26-32. 89.Mahmoud, M. I. 1994. Physicochemical and functional propertyes of protein hydrolysates in nutriational products. Food Technology 48 (10): 89-95. 90.Maines, M.D,, Costa, L.G., Reed, D.J,, Sassa, S. and Sipes, I.G. 1999. Current protocols in toxicology. John Wiley and Sons, New York. 91.Manlry, C. H. and Ahmedi, S. 1995. The development of processs flavors. Trends in Food Sci. & Technol. 6: 46-51. 92.Mannel, D. N. and Echtenacher, B. 2000. TNF in the inflammatory response. Chem. Immunol. 74: 141 – 161. 93.Meisel, H. 1997. Biochemical properties of regulatory peptides derived from milk proteins. Biopolymers 43(2): 119-128. 94.Meisel, H. 1998. Overview on milk protein-derived peptides. Int. Dairy J. 8: 363-373. 95.Meisel, H. and Frister, H. 1988. Chemical characterization of a caseinophosphopeptides isolated from in vivo digests of a casein diet.Biol. Chem. Hoppe-Seyler.369: 1275-1279. 96.Meisel, H. and Schlimme, E. 1990. Milk proteins: precursors of bioactive peptides. Trends Food Sci. Technol. 8: 41-43. 97.Migliore-Samour, D. and Jolles P. 1988. Casein, a prohormone with an immunomodulating role for the newborn. Experientia 44(3): 188-193. 98.Migliore-Samour, D., Floch, F. and Jolles, P. 1989. Biologically active casein peptide implicated in immuneomodulation. J. Dairy Res. 56: 357-363. 99.Miyauchi, H., Hashimoto, S.I., Nakajima, M. and Shinoda, I. 1998. Bovine lactoferrin stimulates the phagocytic activity of human neutrophil: identification of its active domain. Cell Immunol 187(1): 34-37. 100.Mohr, J.A., Leu, R. and Mabry, W. 1970. Colostral leukocytes. J. Surg. Onc. 2, 163 – 167. 101.Morato, A. F., Carreira, R. L., Junqueira, R. G. and Silvestre, M. P. C. 2000. Optimization of casein hydrolysis for obtaining high contents of small peptides: use of subtilisin and trypsin. J. Food Compos. Anal. 13: 843-875. 102.Moon, D. O., Park, S. Y., Choi, Y. H., Kim, N. D., Lee, C. and Kim, G. Y. 2008. Melittin induces Bcl-2 and caspase-3-dependent apoptosis through downregulation of Akt phosphorylation in human leukemic U937 cells. Toxicon 51:112 – 120. 103.Munker, R. and Koeffler, H.P. 1987. Tumor necrosis factor: recent advances. Klin Wochenschr 65(8): 345-52. 104.Mykanen, H. M. and Wassermann, R. H. 1980. Enhanced absorption of calcium by casein phosphopeptides in Rachitic and normal chicks. J. Nutr. 110: 2141-2148. 105.Nakadai, T., Nansuno, S. and Iguchi. 1972. The action of peptidase from Aspergillus oryzae in digestion of soybean protein. Agric. Biol.Chem. 36: 261. 106.Nakamura, Y., Yamamoto, N., Sakai, K., Okubo, A., Yamazaki, S. and Takano, T. 1995. Antihypertensive effect of sour milk and

peptides isolated from it that are inhibitors to angiotensin converting enzyme. J. Dairy Sci. 78: 1253-1257. 107.Narambuena, C.F, Ausar, F.S., Bianco, I.D. Beltramo, D.M., and Leiva, E.P.M. 2005 J. Agric. Food Chem. 53: 459. 108.Newton, E.R. 2004. Breast milk—the gold standard. Clin. Obstet. Gynecol. 47, 632 – 642. 109.Newby, T.J., Stokes, C.R., and Bourne, F.J. 1982. Immunological activities of milk. Vet. Immol. Immunopath. 3, 67 – 94. 110.Old, L. J. 1988. Tumor necrosis factor. Sci. Am., 258: 59 – 75. 111.Onozaki, K., Urawa, H., Tamatani, T., Iwamura, Y., Hashimoto, T., Baba, T., Suzuki, H., Yamada, M., Yamamoto, S. and Oppenheim, J.J. 1988. Synergistic interactions of interleukin 1, interferon-beta, and tumor necrosis factor in terminally differentiating a mouse myeloid leukemic cell line (M1). Evidence that interferon-beta is an autocrine differentiating factor. J Immunol 140(1): 112-119. 112.Orejana, F. M. and Liston, J. 1982. Agents of proteolysis and it is inhibition in patis (fish sauce) fermentation. J. Food Sci. 47: 198-203. 113.Otani, H. and Futakami, M. 1996. Modification of nitrite production of thioglycolate-elicited mouse peritoneal macrophages by bovine casein digests. Food Agric Imunol 8(1): 56-59. 114.Panesar, P. S., Kennedy, J. F., Gandhi, D. N., and Bunko, K. 2007. Bioutilisation of whey for lactic acid production. Food Chem.105:1-14. 115.Pakkanen, R. and Aalto, J. 1997. Growth factors and antimicrobial factors of bovine colostrum. Int. Dairy J. 7:285 – 297. 116.Paulson, D. J., Wilson, R. L. and Spatz, D. 1984. Cross-flow membrane technology and its application. Food Tech. 38: 77-91. 117.Payne, C. M., Bernstein, C., Bernstein, H., Gerner, E. W. and Garewal, H. 1999. Reactive nitrogen species in colon carcinogenesis. Antioxid Redox Signal, 1: 449 – 67. 118.Pestka, S., Langer, J.A., Zoon, K.C. and Samuel, C.E. 1987. Interferons and their actions. Annu Rev Biochem 56: 727-777. 119.Petersen, R. B. 1981. The impact of the enzymic hydrolysis process on recovery and use of proteins.In Enzymes and Food Processing.G.G.Birch, N. Blakebrough, and K. J. Parker. (Ed). : 149.Applied Science Publishers Ltd., London, U.K. 120.Pintado, M. E., Pintado, A. E. and Malcata F. X. 1999. Controlled whey protein hydrolysis using two alternative proteases. J. Food Fng. 42: 1-13. 121.Playford, R. J. 2001. Peptide therapy and the gastroenterologist: colostrum and ilk-derived growth factors. Clinical Nutrition 20 (Supplement 1): 101-106 122.Powrie, F. and Coffman, R.L. 1993. Cytokine regulation of T-cell function: potential therapeutic intervention. Immunology Today 14(6): 270-274. 123.Quagila, G. B. and Orban, E. 1987. Enzymic solubilisation of sardine (Sardina pilchardus) by comm.ercial protease. J. Sci. Food Argic. 38: 263-269. 124.Quigley, J.D. and Drewr, J.J. 1998. Nutrient and immunity transfer from cow to calf pre- and post-calving. J Dairy Sci;8: 2779 – 90. 125.Ralph, P., Harris, P.E., Punjabi, C.J., Welte, K., Litcofsky, P.B., Ho, M.K., Rubin, B.Y., Moore, M.A. and Springer, T.A. 1983. Lymphokine inducing " terminal differentiation " of the human monoblast leukemia line U937: a role for interferon- γ . Blood 62(6): 1169-1175. 126.Rebeca, B. D., Pena-Vera, M. T. and Diaz-castaneda, M. 1991. Production of fish protein hydrolysates with bacterial protease, yield and nutritional value. J. Food Sci. 56(2): 309-314. 127.Reber, A. J., Lockwood, A., Hippen, A. R. and Hurley, D. J. 2006. Colostrum induced phenotypic and trafficking changes in maternal mononuclear cells in a peripheral blood leukocyte model for study of leukocyte transfer to the neonatal calf. Vet. Immunol. Immunopathol. 109:139 – 150 128.Richard, A. G., Thomas, J. K. and Barbara, A. O. 2000. Immunology Kuby 4th ed, p7. W. H. Freeman and Company, New York. 129.Rival, S. G., Fornaroli, S., Boeriu, C. G. and Wichers, H. J. 2001a. Caseins snd casein hydrolysates. I.lipoxygenase inhibitory properties. J. Agric. Food Chem. 49: 287-294. 130.Rival, S. G., Boeriu, C. G. and Wicher, H. J. 2001b. Casein and casein hydrolysates. II. antioxidative properties and relevance to lipoxygenase inhibition. J. Agric. Food Chem. 49: 295-302. 131.Ronge, H. and Blum, J.W. 1988. Somatomedin C and other hormones in dairy cows around parturition, in newborn calves and in milk. J. Anim. Physiol. Anim. Nutr. 60, 168 – 176. 132.Salgame, P., Abrams, J.S., Clayberger, C., Goldstein, H., Convit, J., Modlin, R.L. and Bloom, B.R. 1991. Differing lymphokine profiles of functional subsets of human CD4 and CD8 T cell clones. Sci 254(5029): 279-282. 133.Satue-Gracia, M. T., Frankel, E. N., Rangavajhyala, N. and German, J. B. 2000. Lactoferrin in infant formulas: effect on oxidation. J. Agric. Food Chem. 48: 4984-4990. 134.Sen, D. P., Sripathy, N. V., Lahiry, N. L., Sreenivasan, A. and Subrahamanyan, V. 1962. Fish hydrolysates. I. Rate of hydrolysis of fish flesh with papain. Food Technol. 5: 138-141. 135.Shih, F. F.1992. Modification of food protein by non-enzymatic methods. In: Biochemistry of Food Protein (B. J. F., Hudson ed.), Ch. 7., Elsevier Applied 136.Shimizu, K., Matsuzawa, H., Okada, K., Tazume, S., Dosako, S., Kawasaki, Y., Hashimoto, K. and Koga, Y. 1996. Lactoferrin-mediated protection of the host from murine cytomegalovirus infection by a T-cell-dependent augmentation of natural killer cell activity. Arch Virol 141(10): 1875-1889. 137.Smith, R. A. and Baglioni, C. 1987. The active form of tumor necrosis factor is a trimer. J. Biol. Chem., 262 (15): 6951 – 6954. 138.Sokolowska, A., Bednarz, R., Pacewicz, M., Georgiades, J. A., Wilusz, T. and Polanowski, A. 2008. Colostrum from different mammalian species— A rich source of colostrinin. Int. Dairy J. 18:204 – 209 139.Spellman, D., Mcevoy, E., Cuinn, G. O. and Fitz Gerald, R. J. 2003. Proteinase and exopeptidase hydrolysis of whey protein: Comparison of the TNBS, OPA and pH stat methods for quantification of degree of hydrolysis. Int. Dairy J. 13: 447-453. 140.Steimer, K.S., Packard, R., Holden, D. and Klagsbrun M. 1981. The serum-free growth of cultured cells in bovine colostrum and in milk obtained later in the lactation period. J Cell Physiol 109(2): 223-34. 141.Stout, R. D. and Suttles, J. 1997. T cell signaling of macrophage function in inflammatory disease. Front. Biosci., 2:197 – 206. 142.Suetsuna, K., Ukeda, H. and Ochi, H. 2000. Isolation and characterization of free radical scavenging activities peptides derived from casein. J. Nutr. Biochem. 11: 128-131. 143.Sundstrom, C. and Nilsson, K. 1976. Establishment characterization of a human histiocytic lymphoma cell line (U-937). Int J Cancer 17(5): 565-577. 144.Sutas, Y., Soppi, E. and Korhonen, H. 1996. Suppression of lymphocyte proliferation in vitro by bovine caseins hydrolyzed with Lactobacillus casei GG-derived enzymes. J. Allergy Clin. Immunol. 98(1): 216-224. 145.Takeda, K., minowada, J. and Bloch, A. 1993. Differential ability of mitogen-stimulated human leukocyte-conditioned media to induce Fc receptors in human leukemia cells. Cell Immunol 79(2): 288-297. 146.Takemura, R. and Werb, Z. 1984. Secretory products of macrophages and their physiological functions. Am. J. Physiol. Cell Physiol., 246: C1-C9. 147.Tamatani, T., Kimura, S., Hashimoto, T. and Onozaki, K. 1989. Purification of guinea pig tumor necrosis factor (TNF): comparison of its antiproliferative and differentiative activities for myeloid leukemic cell lines with those of recombinant human TNF. J Biochem 105(1): 55-60

148.Thompson, A(ed). 1991. The Cytokine Handbook. p.201 – 214. Academic Press: London. 149.Tokuyama, Y. and Tokuyama, H. 1993. Purification andid entification of TGF-b2-relatedgrowth factor from bovine colostrum. J Dairy Res 60, 99 – 109. 150.Vacher, P.-Y. and Blum, J.W., 1993. Age-dependency of insulin-like growth factor I, insulin, protein and immunoglobulin concentrations and g-glutamyl-transferase activity in first colos trum of dairy cows. Milk Sci. Int. 48, 423 – 426. 151.Van Beresteijn, E. C., Peeters, R. A., Kaper, J., Meijer, R., Robben, A. and Schmidt, D. 1994. Molecular mass distribution, immunological properties and nutritive value of whey protein hydrolysates. J. Food Prot. 57: 619-625. 152.Wahl, S. M., McCartney-Francis, N., Chan, J., Dionne, R. and Ta, L. 2003. Orenstein JM. Nitric oxide in experimental joint inflammation. Benefit or detriment? Cells Tissues Organs, 174: 26-33. 153.Wang, S.Y., Hsu, M.L., Hsu, H.C., Tzeng, C.H., Lee, S.S., Shiao, M.S. and Ho, C.K. 1997. The anti-tumor effect of Ganoderma lucidum is mediated by cytokines released from activated macrophages and T cells. Int J Cancer 70(6): 699-705. 154.Wang, W.P., Iigo, M., Sato, J., Sekine, K., Adachi, I. and Tsuda H. 2000. Activation of intestinal mucosal immunity in tumor-bearing mice by lactoferrin. Jpn J Cancer Res 91(10): 1022 – 1027. 155.Watson, D.L. 1980. Immunological functions of the mammary gland and its secretion—comparative review. Aust. J. Biol. Sci. 33, 403 – 422. 156.Whitaker, J.R. and Tannenbaum, S.R. 1977. Food proteins. AVI publishing company, INC. USA. 157.Wright, S.C., Kumar, P., Tam, A.W., Shen, N., Varma, M. and Larrick, J.W. 1992. Apoptosis and DNA fragmentation precede TNF-induced cytolysis in U937 cells. J Cell Biochem 48(4): 344-355. 158.Wu, H.C., Pan, B.S., Chang, C. L. and Shiau, C. Y. 2005. Low-molecular-weight peptides as related to antioxidant properties of chicken essence. Journal of food and Drag analysis. 13(2): 176-183. 159.Yamauchi, K., Tomita, M., Giehl, T. J. and Ellison, R.T. 1993. Antibacterial activity of lactoferrin and a pepsin-derived lactoferrin peptide fragment. Infect. Immun. 61: 719-728. 160.Yamada, Y., Satio, S. and Morikawa, H. 1998. Hepatocyte growth-factor in human breast milk. Am J Reprod Immunol. 40:112 – 20. 161.Yoo, Y.C., Watanabe, R., Koike, Y., Mitobe, M., Shimazaki, K.I., Watanabe, S. and Azuma, I. 1997. Apoptosis in human leukemic cells induced by lactoferricin, a bovine milk protein-derived peptide: involvement of reactive oxygen species. Biochem Biophys Res Comm 237(3): 624-628. 162.Zinn, S.1997. Bioactive components in milk: introduction. Livest. Prod. Sci. 50:101-103.