# Información técnica-científica internacional.

# Relación del calostro bovino y/o sus ingredientes como suplemento alimenticio en diversas enfermedades

Nota: El calostro bovino no es un medicamento ni está clasificado como tal, tampoco está demostrado medicamente que cure o alivie ninguna enfermedad.
El uso y el consumo de calostro bovino es una decisión personal y es responsabilidad de quien lo recomienda y de quien lo usa.
Estos trabajos aquí incluidos son responsabilidad exclusiva de (los) autor(es) y son presentados con la única intención de educar y como tópicos de interés general, no es intención de la compañía presentarlos como consejo o soporte médico por lo tanto la compañía Schutze-Segen no es responsable en ningún sentido de su contenido.

## Alergias


LeFranc-Millot C, Vercaigne-Marko D, Wal J. -M, et al. (1996) Comparison of the IgE titers to bovine colostral G immunoglobulins and the F(ab')2 fragments in sera of patients allergic to milk. Int Arch Allergy Immunol. 110:156-162.

Savilahti E, Tainio VM, Salmenpera L, Arjomaa P, Kallio M, Perheentupa J, Siimes MA. (1991) Low colostral IgA associated with cow's milk allergy. Acta Pediatr Scan. 80:1207-1213.

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Delespesse, G. Polypeptide factors from colostrum. US Patent #5,371,073 (1994). IgE (the immunoglobulin involved in allergic response) binding factors (IgE-bf) and IgE suppressor activity (IgE-SF) obtained from colostrum have been successfully used to treat allergies.

Collins, AM, et al. Bovine milk, including pasteurized milk, contains antibodies directed against allergens of clinical importance to man. International Archives of Allergy and Applied Immunology 96:362-367 (1991). The presence of antibodies against many of the most common allergies in man, including ryegrass pollen, house dust mites, Aspergillus mold and wheat gluten, were detected in bovine colostrum.

Elrod, KC, et al. Lactoferrin, a potent tryptase inhibitor, abolished late-phase airway responses in allergic sheep. American Journal of Respiratory Critical Care Medicine 156:375-381 (1997). Tryptase, a digestive enzyme, has been implicated in various aspects of asthma, including bronchoconstriction and airway hyperreactivity. Lactoferrin has been shown to inhibit tryptase activity, thus relieving the symptoms of asthma.

Goldman, AS, et al. Anti-inflammatory properties of human milk. Acta Paediatrica Scandinavica 75(5):689-695 (1986). The major anti-inflammatory components found in human milk (and bovine colostrum) include anti-proteases, lactoferrin, lysozyme, secretory IgA, and a number of antioxidants, including cysteine, ascorbate, alpha-tocopherol and beta-carotene.

Murphey, DK, Buescher, ES. Human colostrum has anti-inflammatory activity in a rat subcutaneous air pouch model of inflammation. Pediatric Research 34(2):208-212 (1993). In an experimental animal model using subcutaneous air pouches in rats, colostrum showed significant anti-inflammatory activity.

Buescher, ES, McWilliams-Koeppen, P. Soluble tumor necrosis factor-alpha (TNF-alpha) receptors in human colostrum and milk bind to TNF-alpha and neutralize TNF-alpha bioactivity. Pediatric Research 44(1):37-42 (1998). The ability of colostrum to modulate the inflammatory response is unique. One of the ways in which it does this is through TNF-a receptor proteins, which are found in colostrum. These bind to TNF-a, which inactivates the TNF-a. TNF-a is the activator of the entire inflammatory cascade, so by controlling its activity, colostrum controls the degree of the inflammatory response and can shut it off altogether.

"Clinical studies show that IgE found in bovine colostrum, may be responsible for regulating allergic response," according to Drs. Tortora, Funke and Cast in Microbiology.

## Alzhaimer

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Amaducci, L, et al. Use of phosphatidylserine in Alzheimer's disease. Annals of the New York Academy of Science 640:245-249 (1991). Supplementation with phosphatidylserine, one of the phospholipids found in BIO-lipid, also produces an improvement in symptoms in Alzheimer's.

Crook, TH, et al. Effects of phosphatidylserine in age-associated memory impairment. Neurology 41(5):644-649 (1991). Patients with age-associated memory impairment showed significant improvement in memory performance tests with phosphatidylserine supplementation over a 12 week period.

Crook, T, et al. Effects of phosphatidylserine in Alzheimer's disease. Psychopharmacology Bulletin 28(1):61-66 (1992). Another study which showed an improvement in symptoms of Alzheimer's with phosphatidylserine supplementation over 12 weeks. The less the impairment, the greater the improvement, suggesting that the earlier phosphatidylserine supplementation is begun in the course of the disease, the better the results will be.

Cross, CE, et al. Oxygen radicals and human disease. Annals of Internal Medicine 107(4):526-545 (1987). Oxygen free radicals, the by-products of normal metabolism, have been implicated in disease processes ranging from carcinogenesis to aging, emphasizing the importance of antioxidants in combating these conditions.

Ames, BN, et al. Oxidants, antioxidants, and the degenerative diseases of aging. Proceedings of the National Academy of Sciences USA 90(17):7915-7922 (1993). Oxidant by-products of metabolism cause significant damage to DNA, proteins and lipids. This damage results in aging and the degenerative diseases associated with aging, such as cancer, cardiovascular disease, immune system

decline, brain dysfunction and cataracts. Antioxidant defenses against these diseases decline with age, necessitating the supplementation of antioxidants in the diet.

## Anti-envejecimeinto


Ballard et. al. "Effects of anabolic agents on protein breakdown." Biochem J, 1983;210:243-249:

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Holbrook, N.J. & Ikeyama, S. "Age-related decline in cellular response to oxidative stress: links to growth factor signaling pathways with common defects." Biochem Pharmacol, 2002;64(5-6):999-1005.

Playford, R.J., et al. "Co-administration of the health food supplement, bovine colostrum, reduces the acute nonsteroidal anti-inflammatory drug-induced increase in intestinal permeability." Clin Sci (Lond), 2001;100(6):627-633.


## Asma


Institute of Chemistry and Biochemistry, Hellbrunner Str. 34, 5020 Salzburg, Austria. Univ.-Prof. Dr. Albert Duschl.

Elrod, KC, et al. Lactoferrin, a potent tryptase inhibitor, abolished late-phase airway responses in allergic sheep. American Journal of Respiratory Critical Care Medicine 156:375-381 (1997). Tryptase, a digestive enzyme, has been implicated in various aspects of asthma, including bronchoconstriction and airway hyperreactivity. Lactoferrin has been shown to inhibit tryptase activity, thus relieving the symptoms of asthma.


## Anti-Inflamatorio


Hanson LA, Mattsby-Baltzer I, Engberg I, Roseanu A, Elverfors J, Motas C. **Anti-inflammatory capacities of human milk: lactoferrin and secretory IgA inhibit endotoxin-induced cytokine release.** *Advances in Experimental Medicine and Biology* 371A:669-672 (1995). Lactoferrin and sIgA [both found in colostrum] inhibit pro-inflammatory cytokines

"Glycoproteins in bovine colostrum inhibit the attachment of the Helicobacter pylori bacteria that cause stomach ulcers. Colostrum contains significant amounts of interleukin-10, a strong inflammation inhibitory agent found significant in reducing inflammation in arthritic joints and injury areas," wrote Dr. Olle Hernell, from the University of Ulmea, Sweden, in Science magazine.

Anti-Microbial (Moldoveanu, Zina, et al, "Antibacterial Properties of Milk; IgA_ Peroxidase-Lactoferrin Interactions" Annals of N.Y. Academy of Science, (1983) Vol. 409, 848-850.

Kim, K. et al, "In Vitro and In Vivo Neutralizing Activity of Human Colostrum and Milk Against Purified Toxins A and B of Clostridium Difficle" Journal of Infectious Diseases (1984) Vol. 150 (1) 57-61.

Wada, N., et al, "Neutralizing Activity Against Clostridium Difficile Toxins in the Supernatant of Cultured Colostral Cells" Infectioius Immunology (1980) Vol. 29, 545-550).

McConnell, M.A.; Brooks, H.J.L.; Borissenko, M.B.; Buchan, G. A comparative study of immunoglobulin feels and anti-inflammatory activity in four milk products. Journal of Dairy Science. Publication forthcoming.

Borody, TJ, et al. Tunnel vision in the bowel. Center for Digestive Diseases (2001). Review of irritable bowel syndrome, including ulcerative colitis and Crohn's disease, and its etiology, including infective agents such as Shigella and Campylobacter. Infections of the gut are difficult to treat because no antimicrobial therapy is available that is effective against Clostridia spores. Only bovine colostrum has proven clinical efficacy in eradicating intestinal pathogens, such as rotavirus, and may help control the infections seen in chronic disorders such as irritable bowel syndrome due to the number of biologically active components in colostrum. The growth factors in colostrum help heal intestinal erosions and ulcerations. It also contains anti-inflammatory factors and is nutrient rich. Colostrum may be used alone or in combination with other anti-inflammatory and/or immune substances. Future research should focus on identifying immune strategies, novel delivery systems and identification of the bioactives in colostrum.

Playford, RJ, et al. Bovine colostrum is a health food supplement which prevents NSAID induced gut damage. Gut 44:653-658 (1999). Although non-steroidal anti-inflammatory drugs (NSAIDs) are very effective in controlling joint pain in arthritis, their use also causes significant, and sometimes fatal, gastrointestinal damage. Supplementation with colostrum, however, significantly reduced and healed injury caused by NSAIDs.

Playford, RJ, et al. Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. Clinical Science 100:627-633 (2001). Another study by Dr. Playford on the ability of colostrum to prevent damage due to NSAID use. This study showed that colostrum also prevents an increase in gastrointestinal permeability due to NSAID use, whereas NSAID use alone without colostrum causes an increase in permeability.

Goldman, AS, et al. Anti-inflammatory properties of human milk. Acta Paediatrica Scandinavica 75(5):689-695 (1986). The major anti-inflammatory components found in human milk (and bovine colostrum) include anti-proteases, lactoferrin, lysozyme, secretory IgA, and a number of antioxidants, including cysteine, ascorbate, alpha-tocopherol and beta-carotene.

Murphey, DK, Buescher, ES. Human colostrum has anti-inflammatory activity in a rat subcutaneous air pouch model of inflammation. Pediatric Research 34(2):208-212 (1993). In an experimental animal model using subcutaneous air pouches in rats, colostrum showed significant anti-inflammatory activity.

Buescher, ES, McWilliams-Koeppen, P. Soluble tumor necrosis factor-alpha (TNF-alpha) receptors in human colostrum and milk bind to TNF-alpha and neutralize TNF-alpha bioactivity. Pediatric Research 44(1):37-42 (1998). The ability of colostrum to modulate the inflammatory response is unique. One of the ways in which it does this is through TNF-a receptor proteins, which are found in colostrum. These bind to TNF-a, which inactivates the TNF-a. TNF-a is the activator of the entire inflammatory cascade, so by controlling its activity, colostrum controls the degree of the inflammatory response and can shut it off altogether.

Britigan, BE, et al. The role of lactoferrin as an anti-inflammatory molecule. Advances in Experimental Medicine and Biology 357:143-156 (1994). While the role of lactoferrin in providing non-specific immunity is well documented, it also plays a role in the anti-inflammatory response through its antioxidant effect.

Conneely, OM. Anti-inflammatory activities of lactoferrin. Journal of the American College of Nutrition 20(Suppl. 5):389S-395S (2001). Lactoferrin inhibits dermal inflammatory cytokine production and

acts as a potent anti-inflammatory protein at local sites of inflammation, including the respiratory and gastrointestinal tracts.

Hayashida K, Kaneko T, Takeuchi T, Shimizu H, Ando K, Harada E. **Oral administration of lactoferrin inhibits inflammation and nociception in rat adjuvant-induced arthritis.** *Journal of Veterinary Medical Science* 66(2):149-152 (2004). Bovine lactoferrin inibited the development of arthritis in a rat experimental system by suppressing TNF-alpha (pro-inflammatory cytokine) and increasing IL-10 (anti-inflammatory cytokine) production.

## Propiedades Anti-Oxidantes

Shigenaga, MK, et al. Oxidative damage and mitochondrial decay in aging. Proceedings of the National Academy of Sciences USA 91(23):10771-10778 (1994). The major source of oxidative damage are oxidants generated by mitochondria in the cells of the body. Mitochondrial function declines with age, including decreased membrane fluidity, proton leakage across the inner mitochondrial membrane, and decreases levels of cardiolipin, an important lipid which supports the functioning of proteins in the inner mitochondrial membrane.

Kurz, DJ, et al. Chronic oxidative stress compromises telomere integrity and accelerates the onset of senescence in human endothelial cells. Journal of Cell Science 117:2417-2426 (2004). Oxidative stress due to the buildup of oxidization by-products has been linked to the onset of cell senescence in blood vessel lining cells by disrupting telomere integrity. Telomeres are the "tails" of the chromosomes, the length of which determine the number of cell divisions a cell can undergo before reaching its limit. Glutathione, a powerful natural antioxidant, is crucial in maintaining telomere integrity.

Borissenko, M. Glutathione: A powerful anti-oxidant found in colostrum. NZMP August 2002. Both glutathione and its chemical predecessors are present in large quantities in colostrum. As glutathione is not absorbed directly, glutathione production in the body can only be accomplished by supplementation with its antecedents, cystine, glycine and glutamic acid, all of which are abundant in colostrum.

Buescher, ES, McIlheran, SM. Antioxidant properties of human colostrum. Pediatric Research 24(1):14-19 (1988). Colostrum reduces ferricytochrome C in polymorphonuclear leucocytes (PMNs) and also disrupts other metabolic and enzymatic activities of PMNs which are crucial in PMN respiratory burst mediation of acute inflammation, showing that colostrum is a powerful antioxidant.

Buescher, ES, McIlheran, SM. Colostral antioxidants: separation and characterization of two activities in human colostrum. Journal of Pediatric Gastroenterology and Nutrition 14(1):47-56 (1992). Colostrum interferes with the production of PMN respiratory burst products in two ways, ascorbate and uric acid.

Boldogh, I, et al. Modulation of 4HNE-mediated signaling by proline-rich peptides from ovine colostrum. Journal of Molecular Neuroscience 20(2):125-134 (2003). Colostrinin down regulates lipid peroxidation, inhibits glutathione depletion and reduces intracellular levels of reactive oxygen species (ROS). This is one more way that colostrum demonstrates antioxidant activity.

Wakabayashi, H, et al. Inhibition of iron/ascorbate-induced lipid peroxidation by an N-terminal peptide of bovine lactoferrin and its acylated derivatives. Bioscience, Biotechnology, Biochemistry 63(5):955-957 (1999). Lactoferrin also plays an important antioxidant role in colostrum by preventing lipid peroxidation.

Satue-Gracia, MT, et al. Lactoferrin in infant formulas: effect on oxidation. Journal of Agriculture and Food Chemistry 48(10):4984-4990 (2000). Commercially modified infant formulas based on cow's milk have significantly less lactoferrin than whole milk, and soy formulas contain none, even though lactoferrin acts as an iron transporter protein. Adding lactoferrin to infant formulas results in the dual

benefit of increased iron absorption and acts as an antioxidant and antimicrobial to extend the shelf life of the formulas.

## Desarrollo atletico

Bovine colostrum supplementation enhances physical performance on maximal exercise tests
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We studied the effects of a food supplement made from bovine colostrum on maximal oxygen uptake and flight times in jump tests in 10 young athletes, seven females and three males, in a double blind cross-over design. Defatted and decaseinated bovine colostrum (400 ml daily) or placebo were administered for 12 days and maximal ergospirometer and jump tests were performed on days 11 and 12. In the placebo group the maximal oxygen uptake on day 12 was 7 % smaller than on day 11, whereas in the colostrum group it did not change. Similarly, in the placebo group the mean flight time in the counter movement jump was 9 ms and in the squat jump 0 ms shorter on day 12 than on day 11.
In the colostrum group the flight time in the counter movement group was 4 ms and in the squat jump 10 ms longer on day 12 than on day 11. Thus colostrum improved significantly the oxygen uptake ($p<0.01$) and the flight times ($p<0.05$) in the maximal ergometer and jump tests performed a day apart. There were no significant changes in the serum concentrations of IGF-1, growth hormone, testosterone, total LDL or HDL cholesterol, ALAT, ASAT, creatine kinase, carboanhydrase III, myoglobin, interleukin-6 or blood cells measured on day 12 between the placebo and colostrum groups.
The present results demonstrate that colostral supplementation in young athletes improves running and jumping performance, when the physical performance is restrained by a previous maximal training bout.
Therefore the use of colostral supplementation is beneficial during heavy training periods in athletes.


Berk LS, Nieman DC, Youngberg WS, et al. (1989) The effect of long endurance running on natural killer cells in marathoners. Medicine and Science in Sports and Exercise. 22:207-212.

Buckley JD, et al. Effect of An Oral Bovine Colostrum Supplement Intact on Running Performance.Abstract from: 1998 Australian Conference of Science and Medicine in Sport, Adelaide, South Australia, October 1998.

Burke E. (1996) Colostrum as an athletic enhancer and help for AIDS. Nutrition Science News.

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Sparling PB, Nieman DC, O'Connor PJ. (1993) Selected scientific aspects of marathon racing: an update on fluid replacement, immune function, psychological factors and the gender difference. Sports Medicine. 15:116-132.

Hofman Z, Smeets R, Verlaan G, Lugt R, Verstappen PA.,Int J Sport Nutr Exerc Metab. 2002 Dec;12(4):461-9. Related Articles, The effect of bovine colostrum supplementation on exercise performance in elite field hockey players. Numico Research, Bosrandweg 20, 6704 PH Wageningen, The Netherlands.

Coombes JS, Conacher M, Austen SK, Marshall PA. Med Sci Sports Exerc. 2002 Jul;34(7):1184-8. Related Articles, Links, Dose effects of oral bovine colostrum on physical work capacity in cyclists. School of Human Movement Studies, University of Queensland, St Lucia, Australia.

Mero, A.; Miikkulainen, H,; Riski, J,; Pakknen, R,; Aalto, J,; Takala, T. Effects of bovine colostrum supplementation on serum IGF-1, IgG, hormone, and saliva IgA during training. Journal of Applied,Physiology. 83(4):1144-1151, April 1997.

J Buckley*, M Abbott, S Martin, G Brinkworth & P Whyte, Abstract from: 1998 Australian Conference of Science and Medicine in Sport, Adelaide, South Australia, October 1998. Effect of an oral bovine colostrum supplement (intact TM ) on running performance. Centre for Research in Education and Sports Science, University of South Australia.

Spagnoli A, Rosenfeld RG, Dept. of Pediatrics, Oregon Health Sciences University, Portland, OR, The mechanisms by which growth hormone brings about growth. The relative contributions of growth hormone and insulin-like growth factors. Endocrinol Metab Clin North Am 1996 Sep; (3):615-31.

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Antonio, J, et al. The effects of bovine colostrum supplementation on body composition and exercise performance in active men and women. Nutrition 17(3):243-247 (2001). Actively training male and female athletes were given colostrum supplementation or placebo for a period of 8 weeks. Subjects receiving colostrum but not placebo showed an increase in lean body mass.

Brinkworth, GD, et al. Effect of bovine colostrum supplementation on the composition of resistance trained and untrained limbs in healthy young men. European Journal of Applied Physiology 9(11):53-60 (2004). Either bovine colostrum or whey protein were given to young men who were either in training or not in training. Those in the training group who received colostrum showed a significantly greater increase in both upper arm circumference and cross-sectional area compared to those receiving whey, while those who were not in training showed no change.

Buckley, JD, et al. Effect of bovine colostrum on anaerobic exercise performance and plasma insulin-like growth factor I. Journal of Sports Science 21(7):577-588 (2003). Athletes in training were given either bovine colostrum or placebo for 8 weeks. Those receiving colostrum showed a significant increase in peak anaerobic power over placebo.

Coombes, JS, et al. Dose effects of oral bovine colostrum on physical work capacity in cyclists. Medicine and Science in Sports and Exercise 34(7):1184-1188 (2002). Dosage studies done on training cyclists showed a small but significant improvement in time trials at doses of 20 g or 60 g/day.

Hofman, Z, et al. The effect of bovine colostrum supplementation on exercise performance in elite field hockey players. International Journal of Sports Nutrition and Exercise Metabolism 12(4):461-469

(2002). Colostrum supplementation in elite field hockey players, both male and female, resulted in improved sprint performance over placebo.

Nieman, DC, et al. Complement and immunoglobulin levels in athletes and sedentary controls. International Journal of Sports Medicine 10(2):124-128 (1989). Blood levels of complements C3 and C4 but not immunoglobulins decreased during periods of rest, graded maximal exercise and recovery in marathon runners.

Nieman, DC, et al. Effects of long-endurance running on immune system parameters and lymphocyte function in experienced marathoners. International Journal of Sports Medicine 10(5):317-323 (1989). Marathon runners experience a disruption of normal immune function after running long distances, a condition which returns to normal levels following 21 hours of recovery.

Berk, LS, et al. The effect of long endurance running on natural killer cells in marathoners. Medicine and Science in Sports and Exercise 22(2):207-212 (1990). A significant decrease in natural killer cell populations were seen in marathon runners following three hours of maximal exercise with full recovery of pre-exercise levels by 21 hours. This correlated with increases in cortisol levels during exercise.

Sparling, PB, et al. Selected scientific aspects of marathon racing. An update on fluid replacement, immune function, psychological factors and the gender difference. Sports Medicine 15(2):116-132 (1993). Negative changes to the immune system during long distance running increase the chances of upper respiratory infections in these athletes for a period following exercise. Proper nutrition, adequate rest and appropriate recover between workouts as well as other measures can lessen the risk.

Burke, ER. Colostrum as an Athletic Enhancer and Help for AIDS. Nutrition Science News May, 1996. While leaky gut is of concern to everyone, it is particularly so for athletes who need to utilize all the nutrients they take in and prevent infection when their immune systems are impaired following exercise. Many athletes suffer irritable bowel syndrome as a result of incomplete digestion of protein supplements. The role of colostrum-derived insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-ß) in healing leaky gut are explored.

Buckley, JD, et al. Bovine colostrum supplementation during endurance running training improves recovery, but not performance. Journal of Science and Medicine in Sport 5(2):65-79 (2002). While supplementation with bovine colostrum does not increase levels of IGF-1 in the blood or initial performance, performance in a second round of exercise significantly improves.

Crooks, C, et al. Bovine colostrum supplementation increases levels of s-IGA in distance runners: a study based on athletes in training for the 2002 Rotorua marathon. Unpublished research. Marathon runners in training were given bovine colostrum or placebo for 12 weeks in a double blind study. Those in the colostrum group showed significantly more secretory IgA (s-IgA) in their saliva than either the placebo group or sedentary controls. The colostrum group also reported a significantly lower rate of upper respiratory infections (URI) during this period.

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Molloy, T, et al. The roles of growth factors in tendon and ligament healing. Sports Medicine 33(5):381-394 (2003). The roles of five different growth factors, IGF-1, TGF-ß, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), in healing tendon and ligament injuries is explored. Each plays a different but vital role in the process.

Sato, K, et al. Improvement of muscle healing through enhancement of muscle regeneration and prevention of fibrosis. Muscle & Nerve 28(3):355-372 (2003). IGF-1 can improve muscle regeneration in injured muscle.

Liang, L, et al. [Effect of cytokines on repair of tendon injury] Zhongguo Xiufu Chongjian Waike Zazhi (Chinese) 14(5):283-285 (2000). Cytokines, such as the growth factors, can accelerate tendon repair.

Mero, A, et al. IGF-I, IgA, and IgG responses to bovine colostrum supplementation during training. Journal of Applied Physiology 93(2):732-739 (2002). Colostrum supplementation increases levels of IGF-1 and IgA in training athletes, but the IGF-1 in the colostrum is not absorbed intact.

Kuipers, H, et al. Effects of oral bovine colostrum supplementation on serum insulin-like growth factor-I levels. Nutrition 18(7-8):165-172 (2002). A study for the International Olympic Committee showed no increase in blood IGF-1 or IGF-bp3 levels after 4 weeks time.

Zimecki, M, et al. Effect of a proline-rich polypeptide (PRP) on the development of hemolytic anemia and survival of New Zealand black (NZB) mice. Archivum Immunologiae et Therapiae Experimentalis 39(5-6):461-467 (1991). Colostrinin (PRP) increased survival in mice susceptible to hemolytic anemia, an autoimmune disease. It is hypothesized the colostrinin induces suppressor cells which slow development of the disease. This suggests that colostrinin may have therapeutic value in treating autoimmune diseases.

## Infecciones bacterianas

In vivo antimicrobial and antiviral activity of components in bovine milk and colostrum involved in non-specific defence. van Hooijdonk AC, Kussendrager KD, Steijns JM.
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The in vivo evidence of the antimicrobial and antiviral activity of bovine milk and colostrum derived components are reviewed with special emphasis on lactoferrin and lactoperoxidase. Their mode of action and the rationale for their application in efficacy trials with rodents, farm animals, fish and humans, to give protection against infectious agents, are described. A distinction is made between efficacy obtained by oral and non-oral administration of these non-specific defence factors which can be commercially applied in large quantities due to major achievements in dairy technology. From the in vivo studies one can infer that lactoferrin and lactoperoxidase are very promising, naturally occurring antimicrobials for use in fish farming, husbandry, oral hygiene and functional foods. Other promising milk-derived compounds include lipids, from which anti-infective degradation products are generated during digestion, and antimicrobial peptides hidden in the casein molecules.

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Christopher-Hennings, J., et al., Immunocompromise in gnotobiotic pigs induced by verotoxin-producing Escherichia coli (OIII:NM). Infect. Immun. 1993. 61: p. 2304-2308.

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Kim, K., et al., In vitro and in vivo neutralizing activity of human colostrum and milk against purified toxins A and B of Clostridium difficile. T. Infect. Dis. 1985. 150: p. 57-61.

Majumdar, A. S., et al., Protective properties of anti-cholera antibodies in human colostrum. Infect. Immun. 1982. 36:p. 962965.

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Morris, J. A., et al., Passive protection of lambs against enteropathogenic Escherichia coli: Role of antibodies in serum and colostrum. T. Med. Microbiol.1980. 13: p. 265-271.

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## Cancer

Milk and dairy products in cancer prevention: focus on bovine lactoferrin
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Abstract
Milk and dairy products constitute an important part of the western style diet. A large number of epidemiological studies have been conducted to determine effects of consumption on cancer development but the data are largely equivocal, presumably reflecting the different included components. It has been proposed that whereas fats in general could promote tumor development, individual milk fats like conjugated linoleic acid could exert inhibitory effects.
There is also considerable evidence that calcium in milk products protects against colon cancer, while promoting in the prostate through suppression of circulating levels of 1,25-dihydroxyvitamin D3.
Whey protein may also be beneficial, as shown by both animal and human studies, and experimental data have demonstrated that the major component bovine lactoferrin (bLF), inhibits colon carcinogenesis in the post-initiation stage in male F344 rats treated with azoxymethane (AOM) without any overt toxicity.
The incidence of adenocarcinomas in the groups receiving 2% and 0.2% bLF were thus 15% and 25%, respectively, in contrast to the 57.5% control value ($P<0.01$ and $P<0.05$, respectively). Results in other animal models have provided further indications that bLF might find application as a natural ingredient of milk with potential for chemoprevention of colon and other cancers.

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## Diabetes

Health-promoting effects of bovine colostrum in Type 2 diabetic patients can reduce blood glucose, cholesterol, triglyceride and ketones. Jun Ho Kim, Wan Sik Jung, Nag-Jin Choi, Dae-Ok Kim, Dong-Hoon Shin, Young Jun Kim Department of food and Biotechnology, Korea University, Jochiwon Chungam 339-700 South Korea, Immunotech Inc Cheonan,Chungam 330-707 South Korea Department of food Science and Technology, Institute of Life Science and Resources, Kyung Hee University, Yongin Gyeonggi 446-701 South Korea April 2008.
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# Factores inmunes

In vitro antiviral activity of lactoferrin and ribavirin upon hantavirus
Murphy ME, Kariwa H, Mizutani T, Yoshimatsu K, Arikawa J, Takashima I.
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Bovine lactoferrin (LF) and ribavirin (Rbv) were tested as antiviral agents against Seoul type hantavirus (SR-11 strain) in vitro.
Hantaviral foci number in Vero E6 cells infected with SR-11 was reduced with LF treatment by 5 days post infection to obtain a 50% effective dose (ED50) of 2500 microg/ml, while pretreatment with LF was highly efficacious having an ED50 of 39 microg/ml. Conversely, 1 h pretreatment with Rbv revealed no inhibition of viral focus formation but could significantly reduce the number of viral foci (ED50: 10 microg/ml) when used from the time of viral infection.
One hour pre-treatment of the cell monolayer with LF and subsequent addition of Rbv revealed a synergistic anti-hantaviral effect against SR-11, <20 FFU/ml as compared to 10(5) foci/ml in the control.
One hour treatment of SR-11 with LF prior to cell inoculation gave an ED50 of 312.5 microg/ml. Whereas, washing the LF-pretreated cell monolayer with PBS demonstrated minimal focus reduction, suggesting LF lightly adheres to cells.
These results indicate that LF has anti-hantaviral activity in vitro and inhibition of virus adsorption to cells which play an important role in revealing the anti-hantaviral activity of LF. This paper reports for the first time the anti-hantaviral effect of LF.
PMID: 11003470 [PubMed - indexed for MEDLINE]


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## Efecto sobre diversos virus (Hepatitis C, Influenza)

Prevention of Influenza Episodes With Colostrum Compared With Vaccination in Healthy and High-Risk Cardiovascular Subjects: The Epidemiologic Study in San Valentino
Clinical and Applied Thrombosis/Hemostasis Vol. 13, No. 2, April 2OO7 130-L36
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From San valentino-Spottore Biomedical Sciences,
The efficacy of a 2-month treatrnent with oral colostrum in the prevention of flu episodes compared with antiinfluenza vaccination was evaluated. Groups induded healthy subjects without prophylaxis and those receiving both vaccination and colostrum. After 3 months of follow up, the number of days with flu was 3 times higher in the non-colostrum group.

Bovine Lactoferrin Inhibits Adenovirus Infection by Interacting with
Viral Structural Polypeptides
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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2003, p. 2688–2691 Vol. 47, No. 8

Effects of orally administered bovine lactoferrin and
lactoperoxidase on influenza virus infection in mice
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Journal of Medical Microbiology (2005), 54, 717–723

Randomized, double-blind, placebo-controlled trial of bovine lactoferrin in patients with chronic hepatitis C
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Antiviral activity of lactoferrin towards naked viruses
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Bovine Lactoferrin Inhibits Adenovirus Infection by Interacting with
Viral Structural Polypeptides
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Inhibitory Activities of Bovine Macromolecular Whey Proteins
on Rotavirus Infections In Vitro and In Vivo
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Lactoferrin Inhibits Hepatitis C Virus Viremia in Patients with Chronic Hepatitis C: A Pilot Study
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Prevention of Influenza Episodes With Colostrum Compared With Vaccination in Healthy and High-Risk Cardiovascular Subjects The Epidemiologic Study in San Valentino
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Lactoferrin inhibits hepatitis C virus viremia in chronic hepatitis C patients with high viral loads and HCV genotype 1b
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Effect of lactoferrin in patients with chronic hepatitis C: Combination therapy with interferon and ribavirin
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Lactoferrin inhibits hepatitis B virus infection in cultured human hepatocytes
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Dose-response trial of lactoferrin in patients with chronic hepatitis C.

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Camel Lactoferrin Markedly Inhibits Hepatitis C Virus Genotype 4 Infection of Human Peripheral Blood Leukocytes
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Lactoferrin Inhibits Hepatitis C Virus Viremia in Patients with Chronic Hepatitis C: A Pilot Study
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# Sistema digestivo

Bovine immunoglobulin concentrate-clostridium difficile retains C difficile toxin neutralising activity after passage through the human stomach and small intestine.
Warny M, Fatimi A, Bostwick EF, Laine DC, Lebel F, LaMont JT, Pothoulakis C, Kelly CP.
Gastroenterology Division, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, Massachusetts 02215, USA. Gut. 1999 Feb;44(2):212-7.
Bovine immunoglobulin concentrate (BIC)-Clostridium difficile is prepared from the colostrum of cows immunised against C difficile toxins and contains high concentrations of neutralising IgG antitoxin. To determine the proportion of BIC-C difficile which survives passage through the human stomach and small intestine. METHODS: Six volunteers with an end ileostomy took 5 g of BIC-C difficile containing 2.1 g of bovine IgG on four occasions: alone, with an antacid, during treatment with omeprazole, and within enteric coated capsules. RESULTS: When BIC-C difficile was taken alone, a mean (SEM) of 1033 (232) mg of bovine IgG was recovered in the ileal fluid representing 49% of the total ingested dose. Bovine IgG recovery was not significantly increased by antacid (636 (129) mg) or omeprazole (1052 (268) mg). The enteric capsules frequently remained intact or only partially opened in the ileal effluent and free bovine IgG levels were low in this treatment group (89 (101) mg). Bovine IgG recovery was higher in volunteers with shorter (less than two hours) mouth to ileum transit times (68% versus 36%, p<0. 05). Specific bovine IgG against C difficile toxin A was detected in ileal fluid following oral BIC. Toxin neutralising activity was also present and correlated closely with bovine IgG levels (r=0.95, p<0. 001). Conclusion: BIC-C difficile resists digestion in the human upper gastrointestinal tract and specific anti-C difficile toxin A binding and neutralising activity was retained. Passive oral immunotherapy with anti-C difficile BIC may be a useful non-antibiotic approach to the prevention and treatment of C difficile antibiotic associated diarrhoea and colitis.

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# Lactoferrina

Lactoferrin and its biological functions. Kanyshkova TG, Buneva VN, Nevinsky GA.
Novosibirsk Institute of Bioorganic Chemistry, Siberian Division of the Russian Academy of Sciences, Novosibirsk, 630090 Russia.
Lactoferrin, a component of mammalian milk, is a member of the transferrin family. These glycoproteins transfer Fe(3+) ions. Lactoferrin is a unique polyfunctional protein that influences cell proliferation and differentiation.
It can regulate granulopoiesis and DNA synthesis in some cells. Lactoferrin inhibits prostaglandin synthesis in human milk macrophages and activates the nonspecific immune response by stimulating phagocytosis and complement. It can interact with DNA, RNA, proteins, polysaccharides, heparin-like polyanions, etc.; in some of its effects, lactoferrin is found in complexes with ligands. It was recently demonstrated that lactoferrin also possesses ribonuclease activity and is a transcription factor.
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This review analyzes possible mechanisms of its polyfunctionality.

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## Sindrome intestinal

Gastrointestinal injury and Colostrum
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Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics but cause gastrointestinal injury. Present prophylactic measures are suboptimal and novel therapies are required. Bovine colostrum is a cheap, readily available source of growth factors, which reduces gastrointestinal injury in rats and mice.
We therefore examined whether spray-dried, defatted colostrum could reduce the rise in gut permeability (a non-invasive marker of intestinal injury) caused by NSAIDs in volunteers and patients taking NSAIDs for clinical reasons. Healthy male volunteers (n = 7) participated in a randomized crossover trial comparing changes in gut permeability (lactulose/rhamnose ratios) before and after 5 days of 50 mg of indomethacin three times daily (tds) per oral with colostrum (125 ml, tds) or whey protein (control) co-administration. A second study examined the effect of colostral and control solutions (125 ml, tds for 7 days) on gut permeability in patients (n = 15) taking a substantial, regular dose of an NSAID for clinical reasons.
For both studies, there was a 2 week washout period between treatment arms. In volunteers, indomethacin caused a 3-fold increase in gut permeability in the control arm (lactulose/rhamnose ratio 0.36±0.07 prior to indomethacin and 1.17±0.25 on day 5, $P < 0.01$), whereas no significant increase in permeability was seen when colostrum was co-administered. In patients taking long-term NSAID treatment, initial permeability ratios were low (0.13±0.02), despite continuing on the drug, and permeability was not influenced by co-administration of test solutions. These studies provide preliminary evidence that bovine colostrum, which is already currently available as an over-the-

counter preparation, may provide a novel approach to the prevention of NSAID-induced gastrointestinal damage in humans.

Treatment of Helicobacter pylori infection in infants in rural Bangladesh with oral immunoglobulins from hyperimmune bovine colostrum.
Casswall TH, Sarker SA, Albert MJ, Fuchs GJ, Bergstrom M, Bjorck L, Hammarstrom L.
Department of Clinical Sciences, Huddinge Hospital, Karolinska Institute,
Sweden. 1: Aliment Pharmacol Ther 1998 Jun;12(6):563-8
BACKGROUND: Antibodies from hyperimmune bovine colostrum have been shown to be effective in treatment against a variety of microorganisms, including Helicobacter pylori in adults. AIM: To test this form of treatment in a small group of H. pylori infected children in a periurban community in Bangladesh.
METHODS: Twenty-four infants, 4-29 months old (mean age 16.57.7 months) and infected with H. pylori, were treated with purified immunoglobulins from
hyperimmune bovine colostrum for 1 month, in a placebo-controlled, double-blind pilot study. Diagnosis was established with 13C-urea breath test (UBT) before and after the treatment period and at a 1-month follow-up. RESULTS: None of the hyperimmune bovine colostrum-treated children became UBT negative. Five children initially positive in the UBT screening spontaneously became negative by the start of the study with hyperimmune bovine colostrum/placebo. At the end of the 1-month study period, three had became positive again.
CONCLUSION: Hyperimmune bovine colostrum does not eradicate H. pylori infection in infants. Transient H. pylori infection is common among infants in high endemic areas, as is re-infection after clearance. This presents obstacles to evaluation of therapeutic investigations in young children in areas where H. pylori is prevalent.

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Rotaviral antibodies in the treatment of acute rotaviral gastroenteritis.
Ylitalo S, Uhari M, Rasi S, Pudas J, Leppaluoto J.
Department of Paediatrics, University of Oulu, Finland. 1: Acta Paediatr 1998 Mar;87(3):264-7
The efficacy of hyperimmune bovine colostrum received from cows immunized with simian rotavirus SA11 in the treatment of rotavirus gastroenteritis was compared in a randomized double-blind trial to

colostrum and ordinary milk preparations. One hundred and thirty-five children aged 6-30 months with rotaviral gastroenteritis received either hyperimmune bovine colostrum (n=42), ordinary colostrum (n=42) or milk (n=41) as a 100 ml solution four times/d for 4 d. Even though the differences were in favour of hyperimmune bovine colostrum in all the variables evaluated [greater weight gain (403 vs 343 g), shorter duration of diarrhoea (3.1 vs 3.6 d), fewer stools during 6 d (11.5 vs 13.6) and fewer stools during the first 3 d (9.3 vs 11.3)], all the differences were statistically insignificant. Differences of this size are clinically unimportant in well-nourished immunocompetent children, but we suggest that the hyperimmune bovine colostrum tested in our trial had some effects in the treatment of acute rotaviral gastroenteritis and should be evaluated further.

# Osteoporosis

Growth factors and cytokines in bone cell metabolism.
Canalis E, McCarthy TL, Centrella M.
Research Laboratory, Saint Francis Hospital and Medical Center, Hartford, Connecticut 06105.
Growth factors regulate the growth and differentiated function of cells. Skeletal cells synthesize fibroblast growth factor, platelet-derived growth factor, insulin-like growth factor, transforming growth factor beta, and additional cytokines. Some of the growth factors produced by bone cells primarily stimulate bone cell replication, whereas others also affect the differentiated function of the osteoblast. Skeletal growth factors also may play a role in the pathogenesis and therapy of metabolic bone disease.

Oral bovine lactoferrin improves bone status of ovariectomized mice. AgroParisTech, Centre de Rechercheen Nutrition Humain de l'Ile de France, UMR914 Nutrition Physiology and Ingestive Behavior, F-75005 Paris, France. blais@agroparistech.fr Am J Physiol Endocrinol Metab. 2009 Jun;296(6):E1281-8. Epub 2009 Mar 31

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Orally administered lactoferrin preserves bone mass and microarchitecture in ovariectomized rats. Guo HY, Jiang L, Ibrahim SA, Zhang L, Zhang H, Zhang M, Ren FZ. College of Food Science and Nutritional Engineering, China Agricultural University, Beijing 100083, China. J Nutr. 2009 May;139(5):958-64. Epub 2009 Mar 25

# Esclerosis multiple

**Treatment of multiple sclerosis with anti-measles cow colostrum** Ebina T, Sato A, Umezu K, Aso H, Ishida N, Seki H, Tsukamoto T, Takase S, Hoshi S, Ohta M.

Previous virological and immunological studies have suggested that multiple sclerosis (MS) is an auto-immune disease triggered by a virus infection. In order to inhibit the growth of measles virus in the patient's jejunum, we obtained an IgA-rich cow colostrum containing anti-measles lactoglobulin resistant to proteases.

This colostrum was orally administered to patients with MS to investigate its effect on the course of the disease. Measles-positive antibody colostrum was orally administered every morning to 15 patients with MS at a daily dosage of 100 ml for 30 days. Similarly, measles-negative antibody (less than 8) control colostrum was orally administered to 5 patients.
As a clinical assessment, disability scores developed by the International Federation of Multiple Sclerosis Societies were used. As a result, of 7 high NT titre (512-5120) anti-measles colostrum recipients 5 patients improved and 2 remained unchanged. Among 8 low NT titre (8-32) anti-measles colostrum recipients 5 patients improved and 3 remained unchanged.
However, of 5 negative NT titre (less than 8) colostrum recipients 2 patients remained unchanged and 3 worsened. No side-effects were observed in colostrum recipients.
These findings suggest the efficacy of orally administered anti-measles colostrum in improving the condition of MS patients (P less than 0.05).
PMID: 6493135 [PubMed - indexed for MEDLINE]

## Efecto sobre piel

Effect of growth factors on cell proliferation and epithelialization in human skin.
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The failure of chronic wounds to heal remains a major medical problem. Recent studies have suggested an important role for growth factors in promoting wound healing. We investigated the mitogenic effect of basic fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), and epidermal growth factor (EGF), comparing their effects with those of media alone (MEM) in a human skin explant model. A stable organ culture system for maintaining the histologic structure of human epidermis for 10 days in vitro was developed. DNA synthesis was measured on Days 1, 3, and 7 of organ culture using [3H]thymidine ([3H]thy) uptake and expressed as cpm/mg dry weight (mean +/- SEM). FGF, IGF-1, and EGF were each capable of stimulating [3H]thy uptake on Day 1 of culture (2372 +/- 335 FGF, 2226 +/- 193 IGF-1, 4037 +/- 679 EGF vs 1108 +/- 70 MEM, P < 0.05). IGF-1 and EGF also stimulated [3H]thy uptake on Days 3 and 7 of culture. The organ culture system was further employed to observe epidermal outgrowth. Longest keratinocyte outgrowth from the explant periphery (simulating epithelial regeneration from the wound edge) was observed on Day 7. EGF resulted in maximum stimulation of epithelial outgrowth (440 +/- 80 microns), followed by FGF (330 +/- 56 microns), IGF-1 (294 +/- 48 microns), and MEM (189 +/- 50 microns). We postulate, therefore, that FGF, IGF-1, and EGF are important mitogens for wound healing and that EGF in particular is capable of stimulating epithelialization.(ABSTRACT TRUNCATED AT 250 WORDS)
PMID: 7543631 [PubMed - indexed for MEDLINE]

## Sida (AIDS) y sus efectos

Cessation of Cryptosporidium-associated diarrhea in an acquired immunodeficiency syndrome patient after treatment with hyperimmune bovine colostrum
N. Engl. J. Med. 1988 318: 1240-1243. Volume 318:1240-1243 May 12, 1988 Number 19
BL Ungar, DJ Ward, R Fayer and CA Quinn
Division of Tropical Public Health, Uniformed Services University of the Health Sciences, Bethesda, Maryland.
Cryptosporidium is a parasite of the human gastrointestinal tract that can cause life-threatening diarrhea in immunodeficient patients. Although more than 80 agents have been tried with occasional anecdotal success, treatment remains primarily limited to hydration. A 38-yr-old homosexual man with antibody to human immunodeficiency virus and Cryptosporidium-related diarrhea is described. The patient excreted 6- 12 L of stool per day for at least 3 mo, 2 of them spent in the hospital. Trials with more than 6 antidiarrheal medications were ineffective. The patient received bovine colostrum hyperimmune to Cryptosporidium by direct duodenal infusion. During infusion, the patient's fecal output decreased to less than 2 L per day, and 48 h after treatment, stools were formed and oocysts to Cryptosporidium were absent. The patient remained asymptomatic for 3 mo. Hyperimmune bovine colostrum offers an exciting new therapy for cryptosporidiosis; controlled trials to establish efficacy should be undertaken and the active factor(s) characterized.

Effect of bovine lactoferrin on a transmissible AIDS-like disease in mice

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AIDS WHO PORJECT

The appearance of AIDS in the early 1980s shook the medical and scientific communities to their core. Prior to this it appeared that modern medicine had infectious disease on the run. Age-old killers like polio and smallpox had been all but eliminated. There was a general feeling that all diseases would be conquered in time, that viruses and other pathogens had met their match at last.

In the quarter century since AIDS first appeared, a great deal has been learned about viruses in general and retroviruses in particular. Many new treatments have emerged for both HIV infection itself and the opportunistic diseases which take advantage of the compromised immune systems of AIDS sufferers. Yet still the cure for the disease eludes us, as does an effective vaccine. According to the Joint United Nations Programme on AIDS and the World Health Organization (WHO), some 25 million people have died of AIDS in those 25 years (that's a million a year), and an estimated 38.6 million are infected with the virus, making it one of the most lethal epidemics in history. In 2005, AIDS claimed 2.4-3.3 million lives, including over 570,000 children(1).

While sub-Saharan Africa has been hardest hit, AIDS is a major problem globally. Over one million are reported to be infected in China and six million in India. More than a half million have died from AIDS in the US, and over a million are infected (2). In Botswana, approximately one in three people in the entire country are infected, and life expectancy has declined from 65 pre-AIDS to only 40 today(3).

Efforts continue to find both a cure for AIDS and an effective vaccine to prevent further AIDS infections. Yet the very nature of retroviruses make them an exceedingly difficult target.

HIV is a single-stranded, positive-sense, enveloped RNA virus. When the virus infects a cell, its RNA is encoded into a double-stranded DNA molecule by a virally encoded reverse transcriptase molecule present in the viral particle. The viral DNA is then integrated into the cellular DNA by a virally encoded integrase enzyme. Often the virus will become latent at this stage, making any antiviral treatment impossible until it once again becomes active. This latency period can last for years. When the virus becomes active, it replicates and produces large numbers of viral particles that are then released to infect other cells.

What is particularly lethal about HIV is that it primarily infects the very cells in the immune system that would normally keep it in check – CD4+ T cells, macrophages and dendritic cells. Infection of CD4+ cells kills in three different ways: direct viral killing of the cells; increased rates of apoptosis (programmed cell death) in infected cells; and targeting of CD4+ cells by CD8 cytotoxic lymphocytes that recognize infected cells and destroy them. This loss of CD4+ cells is cumulative, and eventually the numbers of CD4+ cells decline below critical levels to where cell-mediated immune function is lost. This leaves the body open to opportunistic infections like Pneumocystis pneumonia and Kaposi's sarcoma, which are what actually kill victims. By robbing the body of its own defenses against it, HIV ultimately kills its host, though at times over a period of years. The virus also mutates rapidly making it difficult to produce an effective vaccine.

The main strategy that the scientific community has used in its attempts to attack HIV reflect the trends used against other pathogens, namely a pharmaceutical strategy to directly attack the virus. As such the antiviral drugs that have been developed to combat HIV have many of the same limitations as previous pharmaceutical drugs developed to combat viral infections. First, they target the infected cells directly, usually by disrupting their ability to replicate the virus. Unfortunately, many uninfected cells in the area of the infected cells are collaterally affected and killed. These drugs are also not effective in all patients. Secondly, all of the antivirals developed to fight HIV have serious side effects, including nausea, diarrhea, vomiting, anemia, and others. Lastly, these drugs are very expensive and thus not available to those who have no insurance coverage or other means of paying for them. This is a major problem in Africa where nearly all AIDS victims have no means to pay for expensive antiretroviral therapies (ART). Combination therapy, which is currently the treatment of choice, costs about $950 a month. Drug companies have lowered their prices in some African

countries to about $500 a month, but this is still far beyond most people's ability to pay. The average monthly salary among middle class wage earners in Uganda, for example, is only about $400 a month(4).

Currently the FDA has approved 29 pharmaceutical drugs for use in the treatment of HIV infection(5). Nearly all inhibit viral replication and include reverse transcriptase inhibitors and protease inhibitors. One, Fuzeon, blocks viral fusion to target cells. HIV has responded by developing resistant strains that are not affected by the drugs, even combinations of them. The future outlook for AIDS treatment from a pharmaceutical perspective remains bleak.

This situation has forced scientists to look elsewhere for effective solutions. ART focuses primarily on attacking infected cells directly. A more effective method would be to stimulate the body's own defenses to attack the virus as well as infected cells. This would make it much more difficult for the HIV to avoid attack through mutation as the immune system has the ability to adapt to the new strains rapidly. One such area of investigation is based on an old remedy, colostrum, the first milk produced by a mammal following the birth of a newborn, which was widely investigated as an antibiotic before modern antibiotics were developed. Specifically one of the components of colostrum, called alternatively PRP (proline-rich polypeptide), transfer factor, dialyzable leukocyte extract (DLE), infopeptides, or colostrinin, has shown great promise. This unique polypeptide (actually a peptide fraction of whole colostrum) has been shown to have immunomodulatory abilities as well as antiviral activity(6).

The principal immunomodulatory action of PRP is to stimulate the maturation of immature thymocytes into either helper or suppressor (also called regulatory) T cells(7,8), depending on the need of the body at the time. Helper T cells present antigens (such as a viral protein) to B lymphocytes, which then produce antibodies to that antigen(9). Helper T cells also help produce memory T cells which retain the "memory" of an antigen in order to expedite the production of antibodies in the event the antigen is reencountered in the future(10). Suppressor T cells, on the other hand, deactivate other lymphocytes after an infection has been cleared to avoid damage to healthy tissues(11). PRP also promotes the growth and differentiation of B cells in response to an infection(12) and the differentiation and maturation of macrophages and monocytes(13). The activity of Natural Killer (NK) cells, cytotoxic cells of the innate immune system, was increased up to 5 times by PRP(14,15,16).

PRP modulates the cytokine system as well. It stimulates the production of a wide range of cytokines, including the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), which initiates the inflammatory cascade of cytokine production, and interferon-gamma (INF-γ), and the anti-inflammatory cytokines interleukins-6 and -10 (IL-6 and IL-10)(17).

PRP functions as a molecular signaling device which works through receptors on target cell surfaces(18) to initiate or suppress the production of specific proteins. It is not species specific; PRP from bovine colostrum works as effectively in humans as PRP from human colostrum(19). As it is a natural product, there are no known side effects or drug interactions, and it can be taken safely by all ages.

Preliminary experimental and clinical studies have shown that PRP holds great promise in combating AIDS. In an experimental *in vitro* system, PRP blocked HIV infection of cells(20). PRP in combination with zidovudine (ZDV), an anti-retroviral drug, is known to be effective in patients suffering from AIDS-Related Complex (ARC), increasing levels of white blood cells, CD8 lymphocytes and IL-2(21). A preliminary study on 25 men with AIDS resulted in clinical improvement or a stabilized clinical condition in 20 of the 25. 12 of 14 anergic (unresponsive to antigenic stimulation) patients demonstrated restored delayed type hypersensitivity to recall antigens within 60 days(22).

Recent research has found that while HIV targets both helper CD4+ and suppressor (or regulatory) CD4+ T cells, they are not suppressed at the same rate. In fact, regulatory T cells decline at a slower rate than helper T cells. As regulatory T cells actively down-regulate the immune response, the disparity between regulatory T cells and helper T cells tends to accelerate the course of the disease and is a strong clinical predictor of CD4+ depletion and death(23). The immunomodulatory effect of PRP could potentially help restore the balance of helper and regulatory T cells.

With this alternative treatment approach in mind, clinical trials were developed to test a new oral product containing colostrum-derived PRP as well as other growth and immune factors, including

trypsin inhibitors, glycoconjugates, orotic acid, lysozyme, and others. Phase I trials were conducted at the Infectious Disease Clinic in Dayton, Ohio, from February to April, 1996. Phase II trials were conducted at the University of Nairobi, Nairobi, Kenya, from March to August 2000.
A total of 39 patients took part in the two studies.
Results of the Nigerian study are summarized in Tables 1-4.

| | Initial | 30 Day | 60 Day | 90 Day |
|---|---|---|---|---|
| **Total Patient Reports** | 35 | 31 | 20 | 17 |
| **Score** | 6.1 | 1.8 | 1.2 | 1.3 |
| **Percent Reduction** | | 69 | 80 | 79 |
| **Expected Phase III % Reduction** | | 50-70 | 60-80 | 75-85 |

Table1. Clinical Symptoms Score.

| | Initial | 30 Day | 60 Day | 90 Day |
|---|---|---|---|---|
| **Total Patient Reports** | 30 | 27 | 13 | 13 |
| **Score** | 4.0 | 2.5 | 2.1 | 1.6 |
| **Percent Reduction** | | 38 | 49 | 60 |
| **Expected Phase III % Reduction** | | 30-50 | 40-60 | 50-70 |

Table 2. Physical Findings Score.

| Initial Total | 30 Day Total | 60 Day Total |
|---|---|---|
| 92,448 | 9,755 | 445 |
| 28,049 | 625 | n/a |
| 33,093 | 239 | n/a |
| 439 | n/a | 175 |
| 59,821 | n/a | 320 |
| 40,381 | 180 | n/a |
| **Expected Phase III** | <1,000 | <500 |
| **% Reduction** | | (<250 at 90 days) |

Table 3. Viral Load. Viral load counts are available only from six patients from the Phase II Trial.

| Initial Total | 30 Day Total | 60 Day Total |
|---|---|---|
| 74 | 153 | 121 |
| 274 | 282 | n/a |
| 245 | 301 | n/a |
| 60 | 47 | n/a |
| 101 | n/a | 117 |
| 211 | n/a | 291 |
| 249 | 271 | n/a |
| **Expected Phase III** | >250 | >250 |
| **% Reduction** | | (>500 at 90 days) |

Table 4. CD4+ Count. Only available for seven patients from the Phase II Trial.

The status of specific clinical conditions in the patients was also monitored during the two studies. Results are shown in Tables 5-12.

| | 30 Days | | | 60 Days | | | 90 Days | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Reduction | Elimination | Total | Reduction | Elimination | Total | Reduction | Elimination |
| **Patients Reporting** | 16 | 14 | 11 | 6 | 6 | 6 | 5 | 5 | 5 |
| **Percent of Total** | | 87.5 | 68.8 | | 100 | 100 | | 100 | 100 |
| **Expected Phase III %Reduction** | | 70-90 | 50-75 | | >80 | >75 | | >80 | >75 |

Table 5. Diarrhea.

| | 30 Days | | | 60 Days | | | 90 Days | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Reduction | Elimination | Total | Reduction | Elimination | Total | Reduction | Elimination |
| **Patients Reporting** | 25 | 22 | 11 | 12 | 10 | 10 | 10 | 9 | 9 |
| **Percent of Total** | | 88 | 80 | | 83 | 83 | | 90 | 90 |
| **Expected Phase III % Reduction** | | 70-90 | 50-75 | | >80 | >75 | | >80 | >75 |

Table 6. Nausea

| | 30 Days | | | 60 Days | | | 90 Days | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Reduction | Elimination | Total | Reduction | Elimination | Total | Reduction | Elimination |
| **Patients Reporting** | 4 | 4 | 3 | 2 | 2 | 2 | 1 | 1 | 1 |
| **Percent of Total** | | 100 | 75 | | 100 | 100 | | 100 | 100 |
| **Expected Phase III % Reduction** | | 70-90 | 50-75 | | >80 | >75 | | >80 | >75 |

Table 7. Vomiting.

| | 30 Days | | | 60 Days | | | 90 Days | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Reduction | Elimination | Total | Reduction | Elimination | Total | Reduction | Elimination |
| **Patients Reporting** | 8 | 6 | 6 | 5 | 4 | 4 | 5 | 4 | 4 |
| **Percent of Total** | | 75 | 75 | | 80 | 80 | | 80 | 80 |
| **Expected Phase III % Reduction** | | 70-90 | 50-75 | | >80 | >75 | | >80 | >75 |

Table 8. Fever.

| | 30 Days | | | 60 Days | | | 90 Days | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Reduction | Elimination | Total | Reduction | Elimination | Total | Reduction | Elimination |
| **Patients Reporting** | 16 | 14 | 11 | 6 | 6 | 6 | 5 | 5 | 5 |
| **Percent of Total** | | 87.5 | 68.8 | | 100 | 100 | | 100 | 100 |
| **Expected Phase III % Reduction** | | 70-90 | 50-75 | | >80 | >75 | | >80 | >75 |

Table 9. Cough.

| | 30 Days | | | 60 Days | | | 90 Days | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Reduction | Elimination | Total | Reduction | Elimination | Total | Reduction | Elimination |
| **Patients Reporting** | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Percent of Total** | | 100 | 67 | | 100 | 100 | | 100 | 100 |
| **Expected Phase III % Reduction** | | 70-90 | 50-75 | | >80 | >75 | | >80 | >75 |

Table 10. Tuberculosis.

| | 30 Days | | | 60 Days | | | 90 Days | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Reduction | Elimination | Total | Reduction | Elimination | Total | Reduction | Elimination |
| **Patients Reporting** | 29 | 23 | 18 | 17 | 14 | 14 | 16 | 12 | 12 |
| **Percent of Total** | | 79 | 62 | | 82 | 82 | | 75 | 75 |
| **Expected Phase III % Reduction** | | 70-90 | 50-75 | | >80 | >75 | | >80 | >75 |

Table 11. Fatigue/Malaise.

| | 30 Days | | | 60 Days | | | 90 Days | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Reduction | Elimination | Total | Reduction | Elimination | Total | Reduction | Elimination |
| **Patients Reporting** | 8 | 6 | 5 | 4 | 4 | 4 | 4 | 4 | 4 |
| **Percent of Total** | | 75 | 62 | | 100 | 100 | | 100 | 100 |
| **Expected Phase III % Reduction** | | 70-90 | 50-75 | | >80 | >75 | | >80 | >75 |

Table 12. Paresthesia.

A comment on the CD4+ results. CD4+ counts are a valid marker of the progression of the HIV infection. However, CD4+ levels are only one measure of wellness. With PRP treatment, CD4+ levels are likely to normalize more slowly than other measures of wellness. Viral load levels may actually increase in the peripheral blood after initiation of treatment as the virus is prevented from entering T cells, particularly in the lymph nodes. This increase in blood levels of HIV causes a temporary drop in CD4+ levels in the peripheral blood. CD4+ levels do increase over time with continued treatment. Normal CD4+ counts for adults range from 500-1500 cells/mm3.

In the Nigerian study, PRP oral spray products were shown to boost T-cell (CD4+) levels to normal or near-normal levels (median 502, none less than 300) in AIDS patients whose T-cell levels prior to treatment were well below normal (median 275) (see Tables 13 and 14). Along with the increase in T-cells came a remission of AIDS symptoms within two days of start of treatment, including nausea, vomiting and diarrhea. Weight gains of up to 5% were recorded (Table 15). Patients taking the PRP spray fared much better in terms of quality of life than did patients on anti-retroviral drugs.

| | **Before** | | **After** | |
|---|---|---|---|---|
| | No. | % | No. | % |
| **150-200** | 17 | 29% | 0 | 0% |
| **201-250** | 10 | 17% | 0 | 0% |
| **251-300** | 21 | 36% | 0 | 0% |
| **301-400** | 4 | 7% | 8 | 14% |
| **401-500** | 4 | 7% | 19 | 33% |
| **501-600** | 2 | 3% | 12 | 21% |
| **601-1000** | 0 | 0% | 19 | 33% |
| **Totals** | 58 | | 58 | |

Table 13. CD4+ counts in 58 experimental subjects before and after application of oral PRP spray.

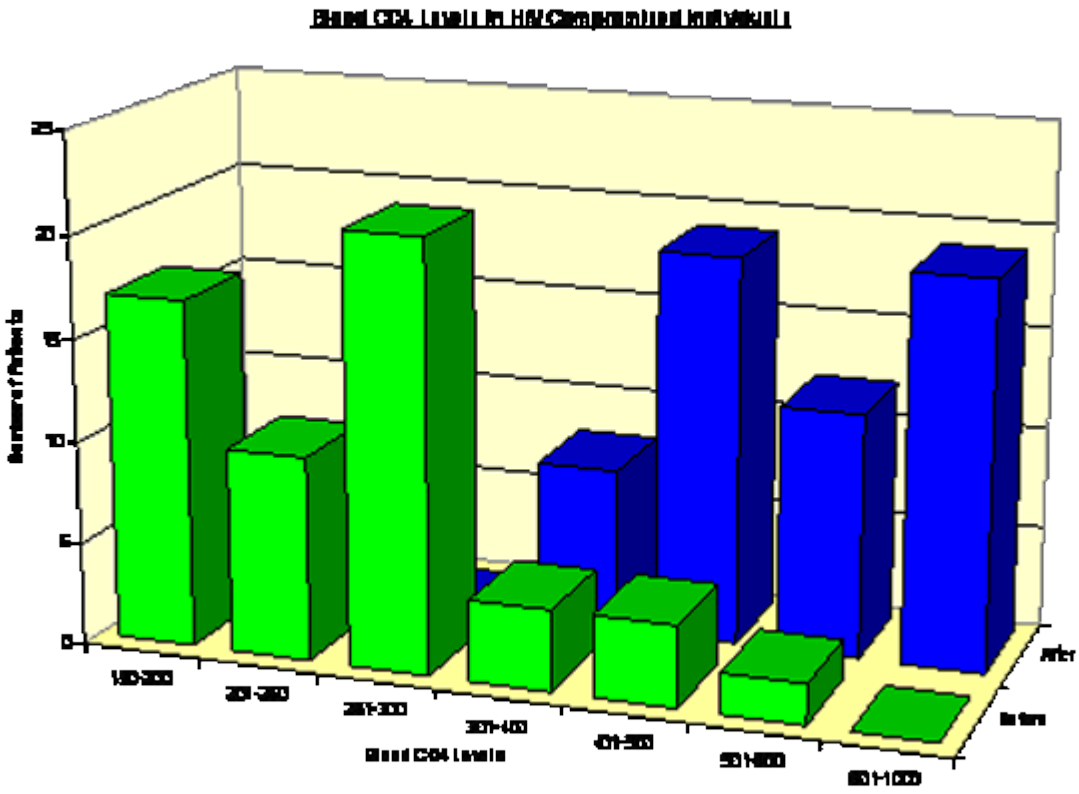

Table 14. CD4+ lymphocyte levels in HIV compromised individuals before and after treatment with PRP oral spray. This bar graph clearly illustrates the marked increase in CD4+ lymphocyte counts in patients with long-term AIDS and severely depleted CD4+ counts after administration of oral PRP spray. Results from Trial 1 held in Nigeria.

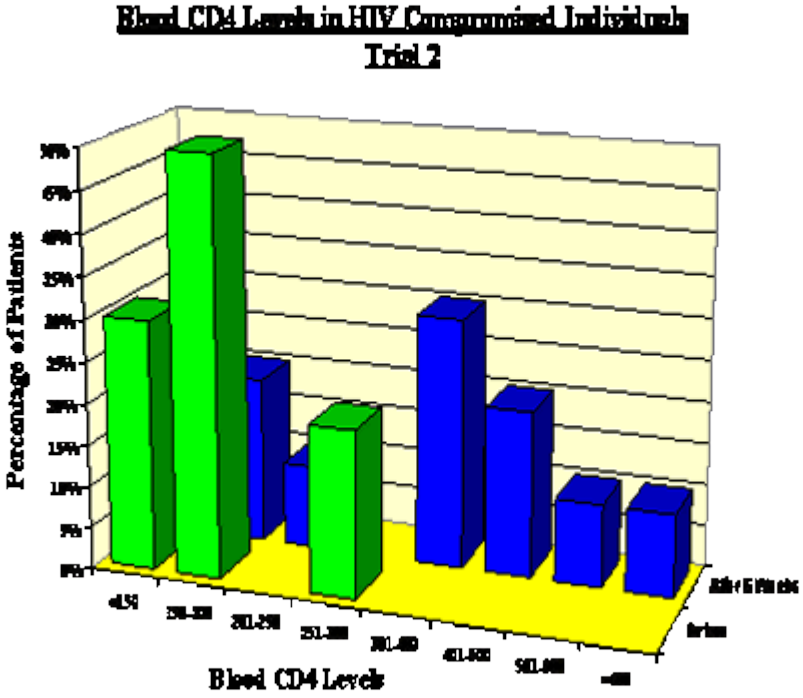


Table 15. Cd4+ lymphocyte levels in HIV compromised individuals before and after treatment with PRP oral spray. These results are from Trial 2 held in Kenya.

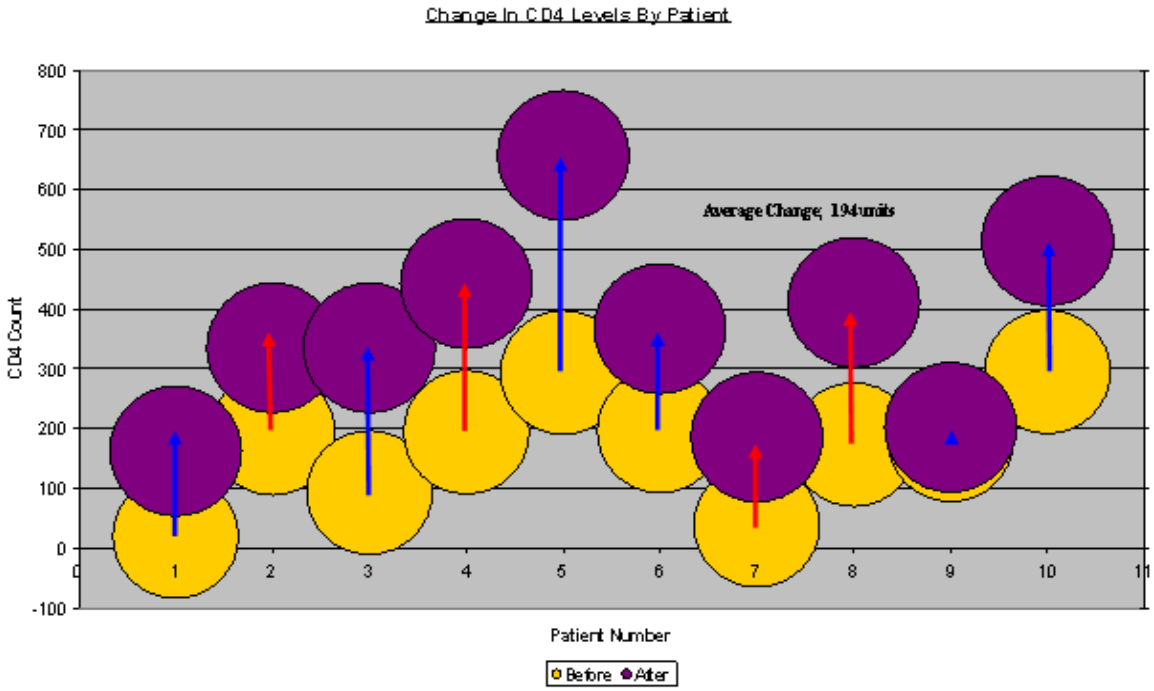


Table 16. A graphical representation of changes in CD4+ lymphocyte levels in patients participating in Trial 2. While levels for some increased over 100% in some cases, what is particularly significant is that levels increased for all participants in the study.

**PRP** **ART**

| Loss/Gain | No. | Loss/Gain | No. |
|---|---|---|---|
| -10 | 1 | -11 | 1 |
| -7 | 1 | -10 | 1 |
| -4 | 1 | -8 | 2 |
| -3 | 1 | -7 | 1 |
| 0 | 2 | -6 | 2 |
| +2 | 1 | -4 | 4 |
| +3 | 2 | -3 | 3 |
| +4 | 1 | -2 | 4 |
| +5 | 1 | -1 | 1 |
| +7 | 1 | 0 | 7 |
| +8 | 1 | +2 | 3 |
| +11 | 1 | +3 | 2 |
| +12 | 2 | +4 | 3 |
| +15 | 1 | +8 | 1 |
| | | +10 | 1 |
| | | +12 | 1 |
| | | +22 | 1 |
| | | +26 | 1 |
| Average +3.4 | | Average +0.3 | |

Table 17. Weight loss/gain for patients on oral PRP or anti-retrovirus therapy.

The results of the African trials confirm the earlier results that an oral PRP spray treatment can be an important alternative or adjunct therapy for AIDS patients. Further studies will be needed to study the long-term effects of the therapy and whether treatment over a longer period can eliminate the virus from the body. Phase III trials are currently underway under the auspices of WHO, and results should soon be available.
While this study used PRP alone, lactoferrin also has powerful anti-HIV effects.

## Polipetidos enriquecidos en prolina (PRP)

Ablashi DV, Levine PH, De Vinci C, Whitman JE Jr, Pizza G, Viza D. Use of anti HHV-6 transfer factor for the treatment of two patients with chronic fatigue syndrome (CFS). Two case reports. *Biotherapy* 9(1-3):81-6 (1996). Transfer factor (PRP) specific to Human Herpes Virus-6 (HHV-6) significantly improved the clinical manifestations of one patient suffering from chronic fatigue syndrome, while another showed no improvement.

Alvarez-Thull L, Kirkpatrick CH. Profiles of cytokine production in recipients of transfer factors. *Biotherapy* 9(1-3):55-59 (1996). Cell cultures from mice responded to HSV infection by secreting large amounts of IL-2 and INF-γ, modest amounts of IL-10, and no IL-4. The same cells responded to concanavalin A and HSV in a similar manner, but instead of IL-2, they produced large amounts of TNF-α, showing that TF (i.e. PRP) treatment selectively affects cytokine production depending on antigenic stimulation.

An Examination of Immune Response Modulation in Humans by Ai/E¹⁰® Utilizing A Double Blind Study. Immune Consultants, Inc., Tucson, Arizona (2001). 20 subjects, 10 men and 10 women, ranging in age from 32-61 participated in a double blind study in which 10 received DLE and the other 10 received placebo. 7 of the 10 receiving the DLE had a significant increase in three major immune markers: NK cell activity, TNF-α levels, and phagocytic index (PI), an indicator of macrophage activity. Those receiving placebo had mixed results
Blach-Olszewska Z, Janusz M.

Stimulatory effect of ovine colostrinine (a proline-rich polypeptide) on interferons and tumor necrosis factor production by murine resident peritoneal cells. *Archivum immunologiae et therapiae experimentalis (Warszava)* 45(1):43-47 (1997). Colostrinine (PRP) from sheep colostrum was found to modulate the production of interferon-beta and tumor necrosis factor-alpha in cultures of mouse cells, indicating it may function as a cytokine.

Boldogh I, Liebenthal D, Hughes TK, Juelich TL, Georgiades JA, Kruzel ML, Stanton GJ.
Modulation of 4HNE-mediated signaling by proline-rich peptides from ovine colostrum. *Journal of Molecular Neuroscience* 20(2):125-134 (2003). PRP, also known as colostrinin, induces mitogenic stimulation as well as a variety of cytokines in peripheral leukocytes. It also possess antioxidant activity in pheochromocytoma (P12) cells, a cancer cell line used for *in vitro* studies. PRP was shown to reduce the amount of 4HNE-protein adducts, reduce intracellular levels of reactive oxygen species, inhibit 4HNE-mediated glutathione depletion, and inhibit 4HNE-induced activation of the molecular signal cascade which results in the production of c-Jun N-terminal kinase (JNK) in P12 cells. This shows that PRP acts as both an antioxidant and a molecular signaling device.

Boldogh I, Aguilera-Aguirre L, Bacsi A, Choudhury BK, Saavedra-Molina A, Kruzel M. Colostrinin Decreases Hypersensitivity and Allergic Responses to Common Allergens. *International Archives of Allergy and Immunology* 146(4):298-306 (2008). Colostrinin (PRP) significantly reduced IgE and IgG1 production, airway eosinophilia, mucin production, and hypersensitivity induced by allergen extracts from ragweed pollen grains and house dust mites. Colostrinin itself is non-allergenic. This study supports the use of colostrinin for the prevention of allergic inflammation in humans.

Boldogh I, Kruzel ML. Colostrinin: an oxidative stress modulator for prevention and treatment of age-related disorders. *Journal of Alzheimer's Disease* 13(3):303-321 (2008). Colostrinin (PRP) is known to have a stabilizing effect on cognitive function in Alzheimer's patients. It does this by preventing the accumulation of amyloid-beta peptide, which has been linked to the progression of Alzheimer's. It accomplishes this by modulating intracellular levels of reactive oxygen species (ROS) through the regulation of glutathione metabolism, activity of antioxidant enzymes and improving the function of mitochondria.

De Vinci C, Levine PH, Pizza G, Fudenberg HH, Orens P, Pearson G, Viza D. Lessons from a pilot study of transfer factor in chronic fatigue syndrome. *Biotherapy* 9(1-3):87-90 (1996). Transfer factor (PRP) was used in a placebo controlled study of 20 chronic fatigue patients. Efficacy of the treatment was measured by clinical monitoring and testing for antibodies to Epstein-Barr and human herpes virus-6 antibodies. Improvement was noted in 12 of the 20 patients.

Domaraczenko B, Janusz M, Orzechowska B, Jarosz W, Blach-Olszewska Z. Effect of proline rich polypeptide from ovine colostrum on virus replication in human placenta and amniotic membrane at term; possible role of endogenous tumor necrosis factor alpha. *Placenta* 20(8):695-701 (1999). PRP stimulated the replication of vesicular stomatitis virus (VSV) in placental and amniotic membrane cultures resistant to VSV, while its effect on sensitized cultures was negligible. This effect was abolished by anti-tumor necrosis factor (anti-TNF) antibodies. This indicates that TNF may be a mediator of virus stimulation by PRP.

Effects of Oral Dietary Supplementation with Ai/E$^{1o}$® Upon Natural Killer (NK) Cell Activity in a Healthy Human Population. Quantum Research, Inc., Scottsdale, Arizona (2001). Dialyzable Leukocyte Extract (DLE) was administered to 12 healthy male and female subjects aged 24-63. Natural Killer (NK) cell activity was prior to initiation of the study and after completion of the study. NK cell activity averaged 30 lytic units (LU) prior to the study and 101 LU following the study for an average increase of 207%.
Fernandez-Ortega, C, Dubed, M, Ruibal, O, Vilarrubia, OL, Menendez de San Pedro, JC, Navea, L, Ojeda, M, Arana, MJ. Inhibition of in vitro HIV infection by dialysable leucocyte extracts. *Biotherapy* 9(1-3):33-40 (1996). A PRP extract from leukocytes inhibits HIV infection in MT-4 cell cultures.

Ferrer-Argote VE, Romero-Cabello R, Hernandez-Mendoza L, Arista-Viveros A, Rojo-Medina J, Balseca-Olivera F, Fierro M, Gonzalez-Constandse R. Successful treatment of severe complicated measles with non-specific transfer factor. *In Vivo* 8(4):555-557 (1994). 10 patients with severe complicated measles, a life-threatening illness, were treated with non-specific transfer factor. 8 of 9 patients experiencing respiratory failure recovered, while the single case of encephalitis was clear of neurologic sequelae within two weeks following the last dose.

Hughes RA. Immunological treatment of multiple sclerosis. *Journal of Neurology* 230(2):73-80 (1983). Transfer factor (PRP) slowed the progession of the disease whereas interferon and levamisole did not.

Inglot AD, Janusz M, Lisowski J. Colostrinine: a proline-rich polypeptide from ovine colostrum is a modest cytokine inducer in human leukocytes. *Archivum immunologiae et therapiae experimentalis (Warszava)* 44(4):215-224 (1996). Colostrinine (PRP) acts as a cytokine inducer in humans, inducing the production of interferon and tumor necrosis factor in human peripheral blood leukocytes in culture.

Iseki M, Aoyama T, Koizumi Y, Ojima T, Murase Y, Osano M. [Effects of transfer factor on chronic hepatitis B in childhood] *Kansenshogaku Zasshi* 63(12):1329-1332 (1989). Nine children with chronic hepatitis B received transfer factor (PRPs) for 3-17 months. Of these, 4 became hepatitis-B negative. After 22-48 months, 6 of the 9 were negative. No side effects were observed.

Janusz M, Lisowski J. Proline-rich polypeptide (PRP)—an immunomodulatory peptide from ovine colostrum. *Archivum immunologiae et therapiae experimentalis (Warszava)* 41(5-6):275-279 (1993). PRP increases the permeability of blood vessels in the skin and causes the differentiation of thymocytes into mature T cells.

Janusz M, Staroscik K, Zimecki M, Wieczorek Z, Lisowski J.
A proline-rich polypeptide (PRP) with immunoregulatory properties isolated from ovine colostrum. Murine thymocytes have on their surface a receptor specific for PRP. *Archivum immunologiae et therapiae experimentalis (Warszava)* 34(4):427-436 (1986). PRP has immunoregulatory properties. It induces the maturation of thymocytes into mature helper or suppressor T cells.

Julius MH, Janusz M, Lisowski J. A colostral protein that induces the growth and differentiation of resting B lymphocytes. *Journal of Immunology* 140(5):1366-1371 (1988). PRP induced resting B cells and supported their progression through the cell cycle to form mature B cells. It had the same action on splenocytes.

Keech A. (2006) Unpublished data. In trials conducted in Nigeria and Kenya, a PRP spray was effective in restoring T cell levels to normal or near normal levels in AIDS patients. Concommitantly, the AIDS symptoms also were alleviated in nearly all patients.
Khan A. Non-specificity of transfer factor. *Annals of Allergy* 38(5):320-322 (1977).

Kirkpatrick CH. Structural nature and functions of transfer factors. *Annals of the New York Academy of Sciences*. 685:362-368 (1993). Transfer factors (PRP) are molecules that "educate" target cells to express cell-mediated immunity. They cause the target cells to express delayed-type hypersensitivity to a given antigen (foreign protein) and produce cytokines which control the immune response.

Kruzel ML, Janusz M, Lisowski J, Fischleigh RV, Georgiades JA. Towards an understanding of biological role of colostrinin peptides. *Journal of Molecular Neuroscience* 17(3):379-389 (2001). PRP (colostrinin) is a potent inducer of leukocyte proliferation and of certain cytokines.

Krylov A, Bogdanenko E, Bogush T, Zhdanov R. The effects of Proline Rich Polypeptide Colostrum Extract treatment on wound healing in a murine skin injury model and assessment of its anti-allergic properties on system anaphylaxis in guinea pigs. *Fourth International Conference on Mechanisms of Action of Nutraceuticals, Tel Aviv, Israel* (2007). In an experimental study done on mice, two wounds were made on the dorsal side of the mice. In one group, one wound was treated with a PRP preparation and the other with distilled water. In the other group, one wound was treated with distilled water, and the other was not treated. The PRP extract improved wound healing about 22%

better compared to the control group. Results were similar to the effect of epidermal growth factor on healing.

Kubis A, Marcinkowska E, Janusz M, Lisowski J. Studies on the mechanism of action of a proline-rich polypeptide complex (PRP): effect on the stage of cell differentiation. *Peptides* 26(11):2188-2792 (2005). PRP affects the differentiation and maturation of cells of the monocyte/ macrophage lineage and may regulate in this way the inflammatory processes in which these cells participate.

Leszek J, Inglot AD, Janusz M, Lisowski J, Krukowska K, Georgiades JA. Colostrinin: a Proline-Rich Polypeptide (PRP) Complex Isolated from Ovine Colostrum for Treatment of Alzheimer's Disease. A Double - Blind Placebo-Controlled Study. *Archivum Immunologiae et Therapiae Experimentalis*. 47(6):377-385 (1999). PRP, derived from colostrum, has shown promise in the treatment of Alzheimer's disease and other dementias, plus it is a very safe drug.

Lisowski J, Wieczorek Z, Janusz M, Zimecki M. Proline-rich polypeptide (PRP) from ovine colostrum. Bi-directional modulation of binding of peanut agglutinin, resistance to hydrocortisone, and helper activity in murine thymocytes. *Archivum immunologiae et therapiae experimentalis (Warszava)* 36(4):381-393 (1988). PRP has a regulatory effect on the immune response. It can cause bi-directional modulation of surface markers and function on T cells from mice. It can reduce binding of peanut agglutinin to PNA+ T cells and increase the binding of peanut agglutinin to PNA- cells. This effect can be reversed by a second application of PRP. It is also able to transform cortisone-resistant T cells to cortisone-sensitive cells and vice versa. Helper T cells initially treated with PRP became helper cells but were transformed into suppressor T cells following a second treatment. This kind of immunoregulatory activity is unique among known immunoregulators.

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Meduri R, Campos E, Scorolli L, De Vinci C, Pizza G, Viza D. Efficacy of transfer factor in treating patients with recurrent ocular herpes infections. *Biotherapy* 9(1-3):61-66 (1996). Herpes-specific transfer factor (PRP) significantly increased the cell-mediated immune response to viral antigens in patients with recurrent ocular herpes infections, and significantly reduced relapses.

Mikulska JE, Lisowski J. A proline-rich polypeptide complex (PRP) from ovine colostrum. Studies on the effect of PRP on nitric oxide (NO) production induced by LPS in THP-1 cells. *Immunopharmacology and Immunotoxicology* 25(4):645-654 (2003). Microglial cells in the brain are related to amyloid beta internalization, the release of inflammatory cytokines, overproduction of nitrogen oxide (NO) and superoxide anion (O2-), and the development of plaques in Alzheimer's disease. PRP regulates the production of cytokines in these cells and inhibits NO and O2- production.

Nitsch A, Nitsch FP. Clinical Use of Bovine Colostrum. *Journal of Orthomolecular Medicine* 13(2) (1998). Low molecular weight components of colostrum (PRPs) were used in a clinical study for the treatment of rheumatoid arthritis with promising results.

Orzechowska B, Janusz M, Domaraczenko B, Blach-Olszewska Z. Antiviral effect of proline-rich polypeptide in murine resident peritoneal cells. *Acta Virologica* 42(2):75-78 (1998). It is known that resident peritoneal (RP) cells from BALB/c female mice express a constitutive non-specific antiviral immunity which is progressively reduced during several days of cultivation in vitro. In this report, we have studied the effect of a proline-rich polypeptide (PRP) isolated from ovine colostrum on the kinetics of vesicular stomatitis virus (VSV) replication in freshly isolated and one-day cultured RP cells. The polypeptide was added to the cells immediately after virus adsorption or one day before or after viral infection. Independently on time of PRP addition, an inhibition of VSV replication (virus titres reduced by up to 4 log units) was observed.

Pizza G, Meduri R, De Vinci C, Scorolli L, Viza D. Transfer factor prevents relapses in herpes keratitis patients: a pilot study. *Biotherapy* 8(1):63-68 (1994). Use of HSV-specific transfer factor (PRP) reduced relapses in herpes ocular infections from 20.1 to 0.51.

Pizza, G, Chiodo, F, Colangeli, V, Gritti, F, Raise, E, Fudenberg, HH, De Vinci, C, Viza, D. Preliminary observations using HIV-specific transfer factor in AIDS. *Biotherapy* 9(1-3):4-47 (1996). 25 HIV infected patients at various stages (CDC stages II-IV) were treated with HIV-specific transfer factor (PRP) for periods of 60-1870 days. All patients were receiving antiviral treatment as well. Clinical improvement or a stabilized clinical condition was observed in 20 of the 25, and 12 of 14 anergic patients showed restored delayed hypersensitivity reactions to recall antigens within 60 days. Treatment was well-tolerated and appears beneficial to AIDS patients.

Pizza G, Viza D, De Vinci C, Palareti A, Cuzzocrea D, Fornarola V, Baricordi R. Orally administered HSV-specific transfer factor (TF) prevents genital or labial herpes relapses. *Biotherapy* 9(1-3):67-72 (1996). Patients with genital or labial herpes received HSV-specific transfer factor (PRP) over a course of 6 months. Controls experienced a relapse index (RI) of 61.2 while those in the experimental group had an RI of 21.4.

Pizza G, Amadori M, Ablashi D, De Vinci C, Viza D. Cell mediated immunity to meet the avian influenza A (H5N1) challenge. *Medical Hypotheses* 67(3):601-8 (2006). As no vaccine can be made ahead of time for a possible bird flu pandemic, cell mediated immunity via specific transfer factor (PRP) may be useful for both the prevention and treatment of infection.

Prasad U, bin Jalaludin MA, Rajadurai P, Pizza G, De Vinci C, Viza D, Levine PH. Transfer factor with anti-EBV activity as an adjuvant therapy for nasopharyngeal carcinoma: a pilot study. *Biotherapy* 9(1-3):109-115 (1996). Nasopharyngeal carcinoma (NPC) has an unsatisfactory overall survival rate. An association between Epstein-Barr virus (EBV) and NPC has been made, so it was hypothesized that anti-EBV transfer factor (PRP) might be used as an adjuvant treatment. The survival rate of NPC patients receiving anti-EBV transfer factor was found to be significantly better than the control group. Although the number of cases in the study was small, adjuvant immunotherapy with anti-EBV transfer factor is of considerable interest.

Raise E, Guerra L, Viza D, Pizza G, De Vinci C, Schiattone ML, Rocaccio L, Cicognani M, Gritti F. Preliminary results in HIV-1-infected patients treated with transfer factor (TF) and zidovudine (ZDV). *Biotherapy* 9(1-3):49-54 (1996). HIV-1 specific transfer factor (an alternative name for PRP) plus zidovudine (ZDV) was tested for efficacy in patients with AIDS-related complex (ARC). Patients receiving both transfer factor and ZDV experienced an increase in white blood cells, CD8+ lymphocytes and IL-2 levels over those receiving ZDV alone.

Rona ZP. Bovine Colostrum Emerges as Immunity Modulator. *American Journal of Natural Medicine* March, 1998.
ABSTRACT: PRP from colostrum can work as a regulatory substance of the thymus gland. It has been demonstrated to improve or eliminate symptomology of both allergies and autoimmune diseases (MS, rheumatoid arthritis, lupus, and myasthenia gravis). PRP inhibits the overproduction of lymphocytes and T-cells and reduces the major symptoms of allergies and autoimmune disease: pain, swelling, and inflammation.

See DM, Gurnee K, LeClair M. An In Vitro Screening Study of 196 Natural Products for Toxicity and Efficacy. *Journal of the American Nutraceutical Association* 2(1):25-39 (1999). A comparative study of 196 natural products showed that many demonstrated toxicity and cytochrome p450 activity (indicative of liver toxicity) while having little or no beneficial action. Some natural products, including *Echinacea*, and glyconutrient-containing products, showed the highest degree of NK cell stimulation. Bovine colostrum showed significant enhancement of NK cell cytotoxicity.

See DM. Transfer Factor™ testing – transfer factor study with 20 cancer patients. 20 cancer patients (levels 3 and 4) with average life expectancy of 3.7 months received 9 capsules of Transfer Factor Plus™ along with other general nutrients. After 8 months, 16 of the 20 were still alive and were either in remission, improving or stabilized. Baseline for NK cell activity was 6.4. After 4 weeks, it increased to 25.7 and after 6 months to 27.6, an increase of 400%.
http://institutelongevitymedicine.blogspot.com/2008/04/20-cancer-patients-study.html

See D, Mason S, Roshan R. Increased tumor necrosis factor alpha (TNF-a) and natural killer cell (NK) function using an integrative approach in late stage cancers. *Immunological Investigations* 31(2):137-153 (2002). A combination of natural products was shown to increase the cytotoxicity of NK cell TNF-a while decreasing DNA damage in patients with late-stage cancer. 20 patients with stage IV end-stage cancer were evaluated using Transfer Factor Plus (3 tabs 3 times/day), IMU-Plus (40 gm/day), IV (50-100 gm/day) and oral (12 gm/day) ascorbic acid, Agaricus Blazeii Murill teas 10 gm/day), Immune Modulator Mix, nitrogenated soy extract, and Andrographis Paniculata (500 mg twice daily). The 16 survivors of the study showed significantly higher NK function and TNF-a levels over baseline. Side effects were limited to occasional diarrhea and nausea, while quality of life improved for all survivors over the six month period of the study. http://www.informaworld.com/10.1081/IMM-120004804

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Wieczorek Z, Zimecki M, Spiegel K, Lisowski J, Janusz M. Differentiation of T cells into helper cells from immature precursors: identification of a target cell for a proline-rich polypeptide (PRP). *Archivum immunologiae et therapiae experimentalis (Warszava)* 37(3-4):313-322 (1989). The precursors of helper T cells belong to a minor thymocyte subset bearing the Thy-1 +/-, H-2+, L3T4-, lyt 2-, CD3- phenotype. PRP induced the production of antigens consistent with mature helper T cells.

Zablocka A, Janusz M, Rybka K, Wirkus-Romanowska I, Kupryszewski G, Lisowski J. Cytokine-inducing activity of a proline-rich polypeptide complex (PRP) from ovine colostrum and its active nonapeptide fragment analogs. *European Cytokine Network* 12(3):462-467 (2001). PRP induces the production of INF-γ, TNF-α, IL-6 and IL-10 in human whole blood cultures.

Zimecki M, Janusz M, Staroscik K, Wieczorek Z, Lisowski J. Immunological activity of a proline-rich polypeptide from ovine colostrum. *Archivum immunologiae et therapiae experimentalis (Warszava)* 26(1-6):23-29 (1978). PRP increased the permeability of blood vessels in the skin and also stimulates or suppresses the immune response depending on the magnitude of the response.

Zimecki M, Staroscik K, Janusz M, Lisowski J, Wieczorek Z. The inhibitory activity of a proline-rich polypeptide (PRP) on the immune response to polyvinylpyrrolidone (PVP). *Archivum immunologiae et therapiae experimentalis (Warszava)* 31(6):895-903 (1983). PRP administered to a test animal before immunization with PVP inhibits the immune response to this antigen. PRP did this by increasing the activity of suppressor T cells and by increasing the generation of new suppressor T cells.

Zimecki M, Lisowski J, Hraba T, Wieczorek Z, Janusz M, Staroscik K. The effect of a proline-rich polypeptide (PRP) on the humoral immune response. I. Distinct effect of PRP on the T cell properties of mouse glass-nonadherent (NAT) and glass-adherent (GAT) thymocytes in thymectomized mice.

*Archivum immunologiae et therapiae experimentalis (Warszava)* 32(2):191-196 (1984). Glass-nonadherent thymocytes are a precursor of helper T cells, and glass-adherent thymocytes are a precursor of suppressor T cells. PRP causes each of these cell types to develop into their lymphocyte types.

Zimecki M, Lisowski J, Hraba T, Wieczorek Z, Janusz M, Staroscik K. The effect of a proline-rich polypeptide (PRP) on the humoral immune response. II. PRP induces differentiation of helper cells from glass-nonadherent thymocytes (NAT) and suppressor cells from glass-adherent thymocytes (GAT). *Archivum immunologiae et therapiae experimentalis (Warszava)* 32(2):197-201 (1984). PRP induces differentiation of both helper and suppressor T cells.

Zimecki M, Pierce CW, Janusz M, Wieczorek Z, Lisowski J. Proliferative response of T lymphocytes to a proline-rich polypeptide (PRP): PRP mimics mitogenic activity of Il-1. *Archivum immunologiae et therapiae experimentalis (Warszava)* 35(3):339-349 (1987). PRP had the same mitogenic effect on T cells as interleukin-1, inducing proliferation of non-antigen specific T cells.

Zimecki M, Hraba T, Janusz M, Lisowski J, Wieczorek Z. Effect of a proline-rich polypeptide (PRP) on the development of hemolytic anemia and survival of New Zealand black (NZB) mice. *Archivum immunologiae et therapiae experimentalis (Warszava)* 39(5-6):461-467 (1991). When PRP was given to New Zealand Black mice showing signs of hemolytic anemia, it significantly lowered the incidence of positive Coombs' reaction and prolonged the mean age of the mice. Hemolytic anemia is an autoimmune disease in these mice, indicating that PRP may have therapeutic value in the treatment of autoimmune disorders in humans.

Zimecki M, Artym J. [Therapeutic properties of proteins and peptides from colostrum and milk] *Postepy Higieny i Medycyny Doświadczalnej* 59:309-323 (2005). Colostrum and milk are rich in peptides and proteins which play an active role in innate immunity. Lactoferrin has antibacterial, antifungal, antiviral, antiparasitic, and antitumor activities. It helps protect the intestinal epithelium, promotes bone growth, and accelerates the recovery of immune system function in immunocompromised animals. PRP has a variety of immunotropic functions, including the promotion of T cell maturation and inhibition of autoimmune disorders.

Zimecki M. A proline-rich polypeptide from ovine colostrum: colostrinin with immunomodulatory activity. *Advances in Experimental and Medical Biology* 606:241-250 (2008). PRP are immunomodulatory peptides from colostrum that promote T cell maturation from early thymic precursors into mature helper cells or mature suppressor cells. They suppressed autoimmune hemolytic anemia in New Zealand black mice. PRP modulate cytokine production in blood. PRP has also been shown to be effective in the treatment of Alzheimer's disease by delaying the progress of the disease.