Immunel™

A white paper on a nutritional extract from bovine colostrum whey

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OVERVIEW

Immunel™ is a proprietary extract from colostral whey (bovine). This white paper describes the current state of knowledge, involving specific biological mechanisms of action, proof-of-concept in animal studies, and clinical data in humans, showing support of anti-bacterial and anti-viral immune functions.

This paper discusses data from research that supports the use of Immunel™ as a protective nutraceutical, with promise in many situations where the support of innate (immediate) immune protection is needed, both in normal daily life and in situations of specific stress.

COLOSTRUM

Colostrum is the biological fluid produced from the mammary glands of female mammals shortly after giving birth. The fluid has a distinct composition different from the milk produced afterwards. The composition of colostrum provides immediate immune protection to the newborn. In humans, some degree of protective passive immunity is transferred to the fetus during gestation to a higher degree than in a number of other mammalian species, and the human colostrum then further supports the continued development of the newborn's immunity. However, in many other mammals, the newborn baby arrives with no immune protection.

Much research provides evidence for transfer of cytokines, immunoglobulin, growth factors, antimicrobial compounds, and maternal immune cells to the newborn via the feeding of colostrum [1-3].

The supportive properties of bovine colostrum when consumed by other mammalian species, including pigs and humans, are well documented in the literature [4-11].

COLOSTRUM CHEMICAL COMPOSITION

Colostral secretions are designed to provide protection critical to neonatal survival during the early days of life as well as sustained growth and development of babies later in their life.

Bovine colostrum is especially rich in immune factors, amino acids, nucleotides and growth factors. Some elements are present in higher quantities in bovine colostrum than in human colostrum.

COLOSTRUM VERSUS IMMUNEL™

Colostrum whey is the liquid remaining after the removal of casein and fat. Whey protein is a well-known nutritional supplement in the sports arena, including body building.

Colostrum whey contains compounds with a direct bactericidal effect. In addition, it also contains compounds that trigger immune defense mechanisms to further help eliminate bacteria and viruses.

Immunel™ is a fat-free, lactose-reduced extract from Colostrum whey, where the immune protective compounds are enriched.

IMMUNEL™ CHEMICAL COMPOSITION

Immunel™ was developed to provide a more concentrated delivery of key bioactive compounds.

These compounds and their known biological properties are listed below in Table 1.

Table 1. Bioactive compounds in Immunel™.

Actives	*Health/Nutrition outcomes*
Proline-Rich-Peptide (PRP)	**Immune modulation, cognitive enhancement, thymus regulation**
Insulin-like Growth Factor-1 (IGF-1)	**Sports nutrition, lean body, cell and tissue repair and rejuvenation**
Transforming Growth Factor (TGF)-β2	**Cell protection, immune enhancement**
Sialic acid	**Immune modulation, brain health, prebiotic**
Nucleotides	**Immune modulation, anti-ageing, stamina**

Immunel™ is a high-potency blend of compounds, allowing multi-facetted mechanisms of actions to support multiple body functions simultaneously.

IMMUNEL SUPPORTS INNATE IMMUNE DEFENSE MECHANISMS

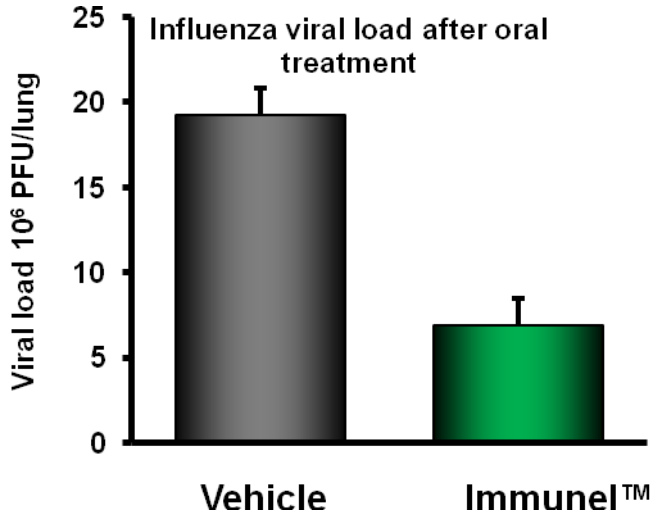
Colostrum reduces flu symptoms comparably to the flu vaccine

The immune modulating compounds in colostrum from farm animals have been receiving attention as substitutes for pharmaceutical drugs in a number of clinical applications [12]. Colostrum provides protection from NSAID-induced intestinal damage [13-16] as well as protection from upper respiratory illness [17-19]. A human study found that nutritional supplementation with colostrum was equally efficient as a vaccine at preventing flu episodes [20].

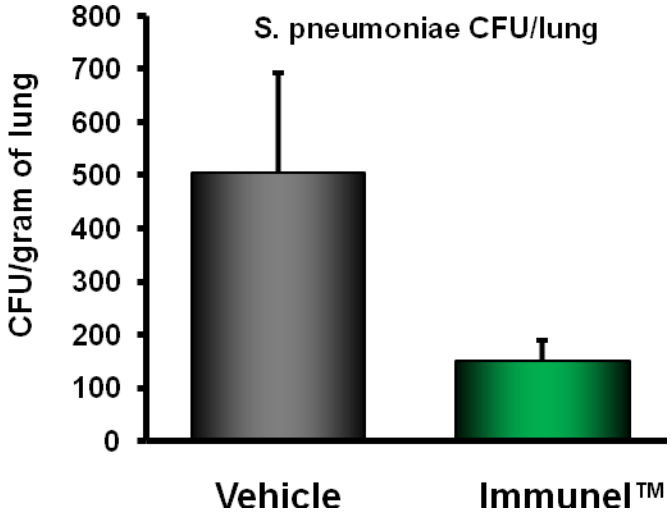
Immunel™ consumption reduced the symptoms and severity of bacterial and viral airway infections in rodents

Two animal studies were conducted on Immunel™ to test whether Immunel™ consumption helped reduce the severity of cold and flu symptoms.

In one study, mice were infected with mouse-adapted influenza virus. Animals treated orally with a single dose of Immunel™ within 24 hours prior to infection showed reduced viral titer in the lungs, compared to control animals.



In another study, mice were infected with Streptococcus pneumonia, which is a human pathogen and causes infections in the upper respiratory tract, sinuses, and eyes. Animals treated orally with two doses of Immunel™ 30 minutes before and 4 hours after infection showed reduced bacterial load at 20 hours after infection, when compared to control animals.



Thus, treatment with Immunel™ showed enhanced bacterial clearance as a result of antimicrobial activity in the animals.

IMMUNEL™ SUPPORTS DISTINCT MECHANISMS OF INNATE IMMUNE DEFENSE REACTIONS.

The 'Innate' part of our immune defense refers to the cellular defenses that act the quickest and most immediate.

Many types of cellular reactions contribute to the immediate efforts to stop microbial invaders from taking hold in our body and causing disease.

These mechanisms include

- → **Phagocytosis, i.e. some of our cells are able to eat bacteria**
- → **Recruiting immune cells into the area of infection**
- → **Killing of our own cells if they have become transformed, such as being infected with a virus.**

When Immunel™ was added to human immune cells in laboratory bioassays, Immunel™ supported all three mechanisms.

Immunel™ supports phagocytosis

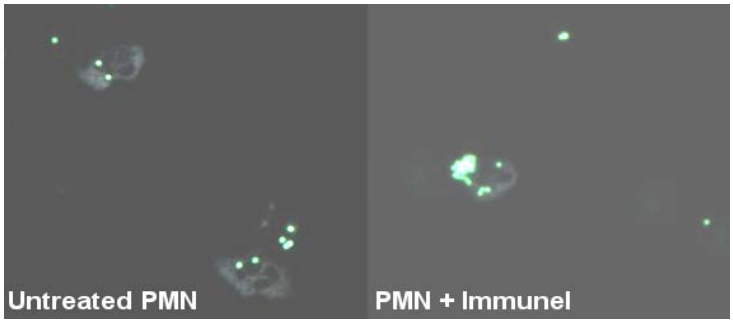
The direct effects of Immunel™ on separate aspects of our innate immune defense were tested in cell-based bioassays using human immune cells.

Phagocytosis (Phago: 'to eat, to consume'; Cyto: cellular) is the process where certain immune cells engulf microbial invaders and destroy them.

Phagocytosis of foreign particles was more robust in the phagocytic cells that had been pre-treated with Immunel™.

In order to test this, human polymorphonuclear (PMN) cells were used.

The pre-treatment with Immunel™ acted almost immediately, and within a few minutes after treating phagocytic cells with Immunel™, more cells were phagocytic, and each phagocytic cell consumed more particles.



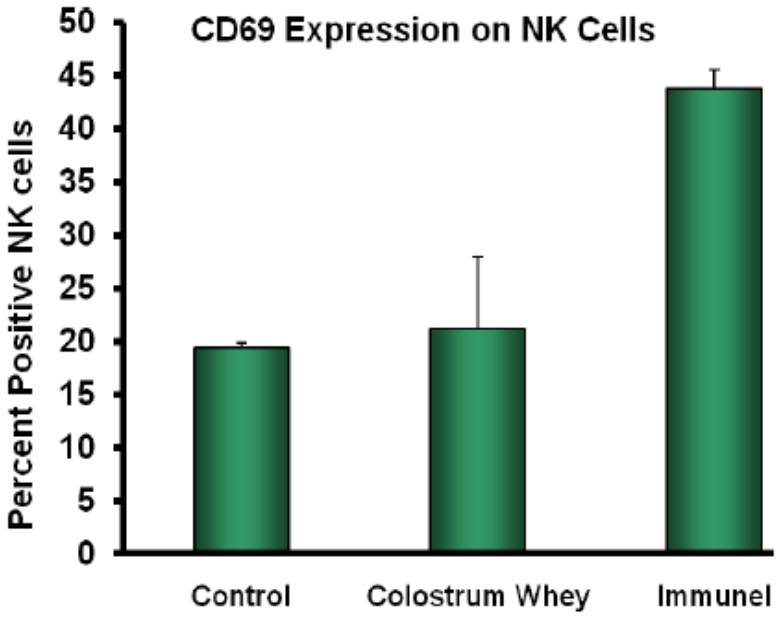
Immunel™ activates Natural Killer (NK) cells.

Another type of immune cells that are able to respond immediately to invading pathogens is called Natural Killer (NK) cells. These cells are able to attach to those of our cells that have become invaded by viruses, or transformed into cancer cells. The killing of the transformed cell can happen via cell-cell contact or by secretion of chemicals such as Perforin which helps destroy the malfunctioning target cell.

Treatment of NK cells with Immunel™ resulted in an activation of the NK cell. The treated NK cells expressed much higher amounts of an activation marker called CD69, which indicates that the NK cells were activated to be more efficient at attacking target cells.

Furthermore, when another well-known stimulus of NK cell activation, namely Interleukin-2 (IL-2) was added to the tests, Immunel™ and IL-2 acted in synergy and produced higher levels of NK cell activation.

This may indicate that when an ongoing immune reaction is happening, and IL-2 is produced, Immunel™ further supports the immune reaction involving NK cells.



Immunel™ also increased the production of Interferon-gamma, which is a cytokine that induces further activation of NK cells and other cell types involved in the innate immune defense.

Immunel™ supports infiltration of phagocytic immune cells in response to microbial challenge

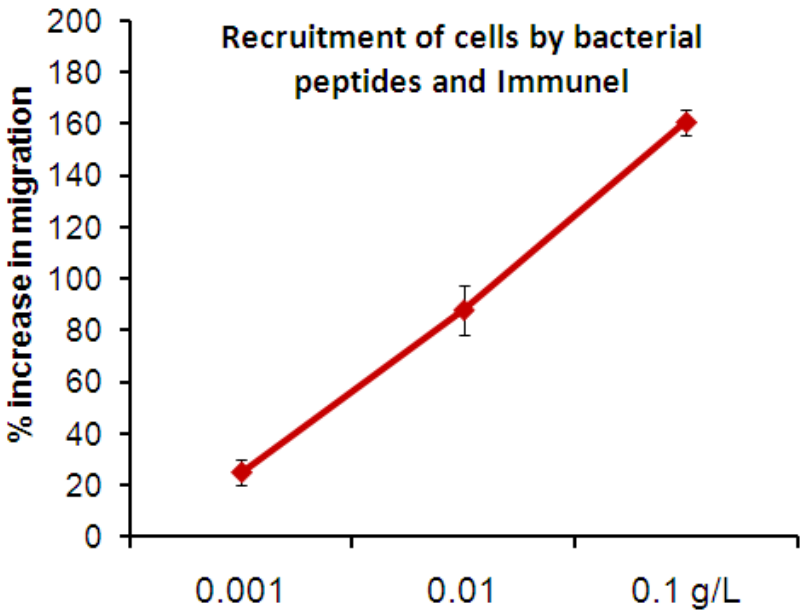
When an invading microbe attacks our cells, and our immune cells respond, chemical signals are sent out to recruit more immune cells to the area. The effective recruitment and increased infiltration of immune cells to an area in need is important for prompt elimination of microbial invaders.

When Immunel™ is consumed it is presented to the immune system from the gut lumen, in conjunction with potentially pathogenic microbes. This may have a protective effect.

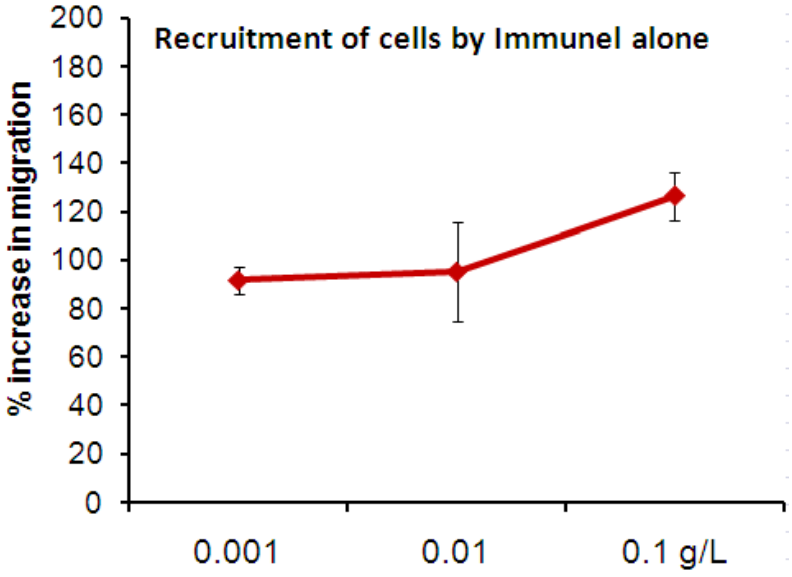
This was tested in a cell-based bioassay using a dual chamber system. Cells were placed in one chamber adjacent to another chamber where pieces of bacterial proteins were placed. Components from the bacterial fragments could seep into the next chamber and result in an increased movement (recruitment) of immune cells into the chamber containing the microbial signal.

When Immunel™ was placed together with the bacterial fragments, an increase in recruitment of immune cells into the chamber containing the bacterial fragments was measured.

This may signify potential benefit from consuming Immunel™, such as strengthening of the gut immune protection, where one of our largest volumes of potential invaders exists.



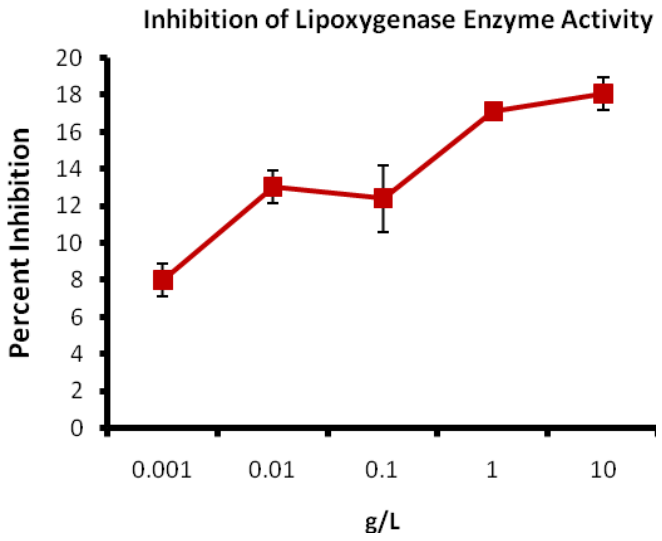
When Immunel™ was placed in the chamber adjacent to the immune cells, in the absence of bacterial fragments, we also saw an increased recruitment into the chamber containing Immunel™. This suggests that when Immunel™ is consumed, more cells are recruited into the gut wall, in preparation to respond to microbial invasion.



IMMUNEL™ HAS ANTI-INFLAMMATORY PROPERTIES

Immunel™ inhibits Lipoxygenase enzyme activity

Selective inhibition of Lipoxygenase enzymatic activity points to an anti-inflammatory role.

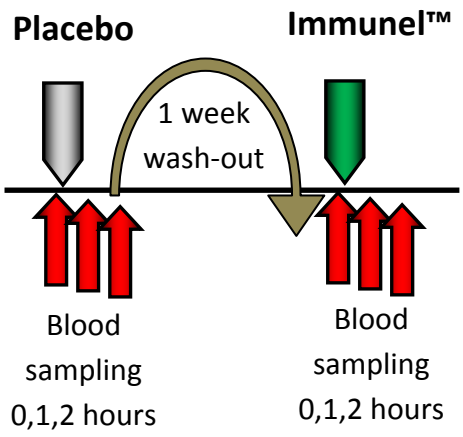


If Immunel™ only had the property of supporting the function of the immediate immune protection, Immunel™ would be a less interesting product. However, since Immunel™ also possesses some natural anti-inflammatory properties from Colostrum, the potentially abrasive result of immune defense reactions are buffered by inhibition of the enzymatic action of Lipoxygenase. This inhibition may further reduce free radical damage naturally associated with immune defenses, in part since the activity of the Lipoxygenase enzyme further produces additional free radicals.

HUMAN CLINICAL DATA

Data from a recent human clinical trial further supports that consumption of Immunel™ induces potent and rapid changes in markers associated with the innate immune defense.

Study design: A randomized double-blinded placebo-controlled cross-over study design was used. Twelve healthy human subjects were tested on two different days at least one week apart. On each test day, subjects were fed either Immunel™ or placebo. At baseline and at 1 and 2 hours after consumption, blood samples were drawn.



The shown sequence is an example only; the sequence in which each person consumed Immunel™ or Placebo for short-term testing was randomized.

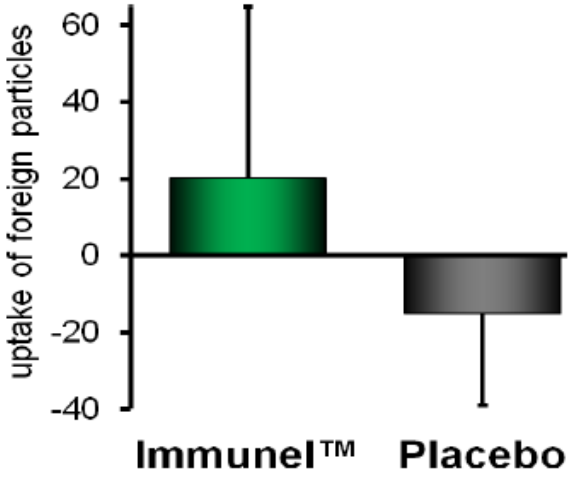
The blood samples were used for testing of two key aspects of human innate immune defense:

- → **Phagocytosis**
- → **Natural killer (NK) cell counts**

Consumption of Immunel™ results in rapid increase in phagocytic activity in humans

Consumption of a single dose of Immunel™ resulted in a rapid increase in the phagocytic activity of human cells tested ex vivo at different time points after consumption. This was in contrast to the reduced phagocytic activity seen on the day when Placebo was consumed by the same people.

The difference in phagocytic activity between Immunel™ and Placebo was statically significant at 2 hours after consuming a single dose ($p<0.02$).



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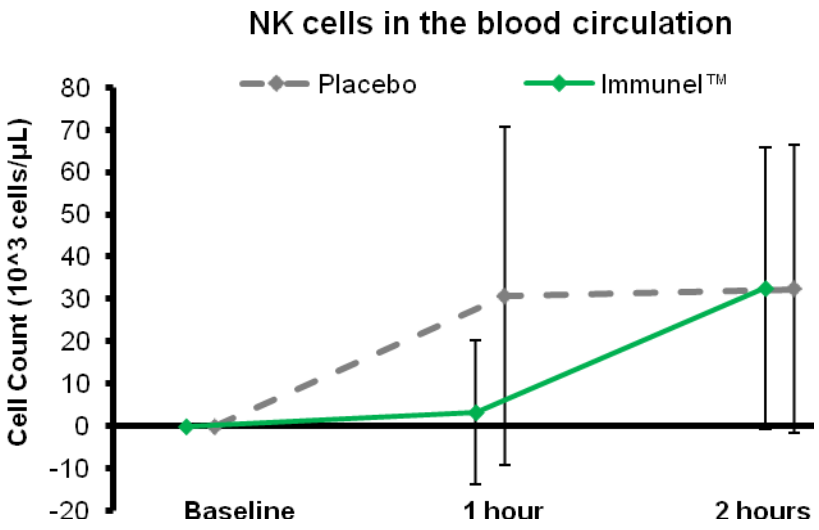
Consumption of Immunel™ provides a rapid, transient support for immune surveillance of human Natural Killer cells

Natural Killer (NK) cells are an important part of our anti-viral defenses, and these cells work primarily by surveying through tissue looking for target cells, which they then kill, either by contact or by secreting certain chemicals. The NK cells have very little activity in the blood circulation.

The study was conducted during the early/mid-morning hours on both study days. The increase in the numbers of circulating Natural Killer (NK) cells, seen with placebo, reflects part of natural circadian (day/night) fluctuations.

The delay in this increase, seen after consumption of Immunel™, is suggestive of increased NK cell trafficking/homing, as a reflection of increased immune surveillance. This reflects that NK cells are retained in tissue more, scavenging for target cells.



CONCLUSION

Mechanistic data, combined with animal studies and human clinical data suggests that Immunel™ induces rapid changes in immune support, including specific mechanisms involved in anti-bacterial and anti-viral defenses.

REFERENCES

1. Goto M, Maruyama M, Kitadate K, Kirisawa R, Obata Y, Koiwa M, Iwai H. Detection of interleukin-1 beta in sera and colostrum of dairy cattle and in sera of neonates. J Vet Med Sci 1997;59:437-41.

2. Yamanaka H, Hagiwara K, Kirisawa R, Iwai H. Transient detection of proinflammatory cytokines in sera of colostrum-fed newborn calves. J Vet Med Sci 2003;65:813-6.

3. Reber AJ, Lockwood A, Hippen AR, Hurley DJ. Colostrum induced phenotypic and trafficking changes in maternal mononuclear cells in a peripheral blood leukocyte model for study of leukocyte transfer to the neonatal calf. Vet Immunol Immunopathol 2006;109:139-50.

4. Bridger JC, Brown JF. Development of immunity to porcine rotavirus in piglets protected from disease by bovine colostrum. Infect Immun. 1981 Mar;31(3):906-10.

5. Pakkanen R, Aalto J. Growth factors and antimicrobial factors of bovine colostrum. Int. Dairy Journal 7:285-297, 1997.

6. He F, Tuomola E, Arvilommi H, Salminen S. Modulation of human humoral immune response through orally administered bovine colostrum. FEMS Immunol Med Microbiol. 2001 Aug;31(2):93-6.

7. Uruakpa FO, Ismond MAH, Akobundu ENT. Colostrum and its benefits: A review. Nutrition Research 2002 22:755-767.

8. Solomons NW. Modulation of the immune system and the response against pathogens with bovine colostrum concentrates. Eur J Clin Nutr. 2002 Aug;56 Suppl 3:S24-8.

9. Boudry C, Buldgen A, Portetelle D, Collard A, Thewis A, Dehoux JP. Effects of oral supplementation with bovine colostrum on the immune system of weaned piglets. Res Vet Sci. 2007 83:91-101.

10. Struff WG, Sprotte G. Bovine colostrum as a biologic in clinical medicine: a review. Part I: biotechnological standards, pharmacodynamic and pharmacokinetic characteristics and principles of treatment. Int J Clin Pharmacol Ther. 2007 Apr;45(4):193-202.

11. Gopal PK, Gill HS. Oligosaccharides and glycoconjugates in bovine milk and colostrum. Br J Nutr. 2000 Nov;84 Suppl 1:S69-74.

12. Séverin S, Wenshui X. Milk biologically active components as nutraceuticals: review. Crit Rev Food Sci Nutr. 2005;45(7-8):645-56.

13. Yoshioka Y, Kudo S, Nishimura H, Yajima T, Kishihara K, Saito K, Suzuki T, Suzuki Y, Kuroiwa S, Yoshikai Y. Oral administration of bovine colostrum stimulates intestinal intraepithelial lymphocytes to polarize Th1-type in mice. Int Immunopharmacol. 2005 Mar;5(3):581-90.

14. Kim JW, Jeon WK, Yun JW, Park DI, Cho YK, Sung IK, Sohn CI, Kim BI, Yeom JS, Park HS, Kim EJ, Shin MS. Protective effects of bovine colostrum on non-steroidal anti-inflammatory drug induced intestinal damage in rats. Asia Pac J Clin Nutr. 2005;14(1):103-7.

15. Purup S, Vestergaard M, O Pedersen L, Sejrsen K. Biological activity of bovine milk on proliferation of human intestinal cells. J Dairy Res. 2007 Feb;74(1):58-65.

16. Playford RJ, Macdonald CE, Johnson WS. Colostrum and milk-derived peptide growth factors for the treatment of gastrointestinal disorders. Am J Clin Nutr. 2000 Jul;72(1):5-14.

17. Lindbaek M, Francis N, Cannings-John R, Butler CC, Hjortdahl P. Clinical course of suspected viral sore throat in young adults: cohort study. Scand J Prim Health Care. 2006 Jun;24(2):93-7.

18. Shing CM, Peake J, Suzuki K, Okutsu M, Pereira R, Stevenson L, Jenkins DG, Coombes JS. Effects of bovine colostrum supplementation on immune variables in highly trained cyclists. J Appl Physiol. 2007 Mar;102(3):1113-22.

19. Crooks CV, Wall CR, Cross ML, Rutherfurd-Markwick KJ. The effect of bovine colostrum supplementation on salivary IgA in distance runners. Int J Sport Nutr Exerc Metab. 2006 Feb;16(1):47-64.