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EXERCISE AND EXPOSURE TO HEAT FOLLOWING BOVINE COLOSTRUM SUPPLEMENTATION: A REVIEW OF GASTROINTESTINAL AND IMMUNE FUNCTION

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Abstract

Colostrum is the first milk produced by mammalian mothers and is essential for the health and survival of the newborn. Bovine colostrum (BC) has greater concentrations of the bioactive components (i.e. immune and growth factors) than those found in human colostrum. As a result, BC supplementation has been recently adopted by many sport competitors as a means of enhancing immune function as well as improving performance. Improvements in physical performance associated with BC supplementation may stem from the ability of BC to maintain gastrointestinal (GI) integrity by decreasing GI permeability. During exercise in the heat, blood flow to the GI tract is reduced that leads to endotoxin leakage into circulation. Endotoxins, such as lipopolysaccharide, can trigger an inflammatory cascade leading to physiological strain that, in turn, increases heat storage and decreases time to exhaustion. GI permeability is lessened during passive heat stress following BC supplementation, but the influence of BC supplementation on GI function during exercise heat stress remains to be determined. The implications of endotoxemia during exercise in the heat is a matter of growing importance and warrants further study given the global increase in ambient temperatures during sport competitions.

Key words: Bioactive milk, endotoxemia, heat tolerance, immunity, athletic performance.

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INTRODUCTION

A mammalian mother has an inherent ability to passively transfer her immunity to the vulnerable newborn within the first 24 hours of its life. The transfer of collected immunological information occurs via colostrum, also referred to as the single most important management factor in offspring health and survival (16). Colostrum is the first mammalian milk produced by the mother during the first few days following parturition (49). In addition to transferring immunity, colostrum provides a complete diet with all essential nutrients and passes on growth factors that contribute to physical development (1). The discovery of this highly concentrated bioactive milk has led to the investigation of its effects on human health and performance. Prior to the development of antibiotic drugs, colostrum was given to weak older animals and humans for immune system support as well as for the treatment of bacterial infections (50). Given that bovine colostrum (BC) has higher concentrations of the bioactive components found in human colostrum, BC supplementation has been popular among athletes as a means of enhancing immune function and physical performance (43, 44).

It has been suggested that the improvements in physical performance associated with BC supplementation stem primarily from the ability of BC to maintain gastrointestinal (GI) integrity by decreasing its permeability and modulating inflammatory responses (27, 31, 54). For instance, during high intensity exercise, blood flow to the GI tract is reduced (11), which heavily compromises the integrity of the intestinal walls (41). Due to a greater decrease in plasma volume, the reduction in blood flow to the gut is exacerbated during exercise in the heat (10, 40) that leads to leakage of endotoxins into circulation (19). Reported consequences of endotoxemia include impairment of muscle contractile function, nausea, diarrhoea, and many others that may contribute to accelerated fatigue and exhaustion (48, 52). With a focus on GI integrity and immune function, we review the literature investigating the effects of BC supplementation on physical performance and heat tolerance.

BOVINE COLOSTRUM

BC, the first milk produced by cows for their developing offspring, provides rich amounts of acquired and innate immune elements, and growth factors that regulate cell proliferation and repair (1). Concentrations of the bioactive components in BC as well as gut permeability of the offspring progressively decline during the first 48 hours after birth (7, 29). Thus, greater consumption of BC immediately following parturition is essential to ensure optimal health and survival of the offspring (16).

Immunoglobulin (Ig) antibodies are the most abundant components of the acquired immune system found in BC (47). Differing concentrations of Ig isotopes have been reported in BC, with IgG as the most plentiful, and to a lesser extent, IgA and IgM (8). Synthesis and secretion of a specific antibody by a B cell occurs in response to an encounter with a foreign antigen, which contributes to the development of our acquired immune system that is transferred from the mother, through passive immunization via BC, to the offspring (47). The transfer of collected immunity is critical for early life offspring survival by ensuring a quick and efficient response to recognizable antigens until its own immune system is fully developed (25). Components that characterize our innate immune system have also been identified in BC that provides the offspring with non-specific recognition and response to pathogens. These include neutrophils, macrophages, oligosaccharides, gangliosides, acute-phase proteins, pro- and anti-inflammatory cytokines, and antimicrobial proteins and peptides (47). Furthermore, growth factors such as insulin like growth factor 1, transforming growth factor beta, as well as epidermal growth factor have also been identified in BC, with the former having the highest concentration (32, 53).

That early life BC consumption is necessary for the health and development of the newborn is not to be refuted. Yet the impact of BC supplementation on health and physical performance in humans remains to be fully understood. The idea is that the plentiful immune and growth factors found in BC will enhance immune function and increase lean mass, that in turn, can lead to performance enhancements and post-exercise recovery effectiveness. Furthermore, potential improvements in physical performance associated with BC supplementation may occur, at least in part, by the ability of BC to lessen the physiological impact of overtraining (21, 44, 45) that has been linked to immune function in elite competitors (33, 42).

BOVINE COLOSTRUM, GASTROINTESTINAL HEALTH AND IMMUNE FUNCTION

The rich source of growth factors in BC (e.g. insulin like growth factor 1, transforming growth factor beta, and epidermal growth factor) initiate growth and repair processes within the GI tract and have a significant role in GI maturation of newborn calves (53). In this light, a number of investigations examined the efficacy of BC supplementation on mammalian GI health and integrity (6, 35, 36, 39). Playford and colleagues (35) introduced pre-treatment with 0.5 or 1 ml of BC prior to administering indomethacin to a restraint rat model of gastric damage, and demonstrated a dose-response reduction in gastric injury. These findings are further supported by other animal studies that investigated the protective qualities of BC against gut damage induced by non-steroidal anti-inflammatory drugs (NSAIDs) (20, 23, 28). In humans, gut permeability was assessed in healthy male volunteers prior to and following five days of NSAID intake either with or without BC in a cross-over design. Results showed that simultaneous intake of BC with NSAID prevented a three-fold increase in gut permeability that was reported with NSAID treatment alone (36). The breakdown of ingested growth factors such as transforming growth factor beta, consumed with BC, is inhibited by casein and other enzyme inhibitors specifically contained within BC that preserve their structure and function, which may explain, at least in part, the maintenance of GI integrity associated with combined BC and NSAID intake (38). The potential for BC supplementation to maintain optimum GI permeability during short-term NSAID treatment offers interesting insight for alternative supplementation strategies to ameliorate endotoxemia associated with exercising in hot weather conditions.

Early intake of BC stimulates and regulates immune responses in newborn calves that are initiated by cytokines such as interleukin (IL)-6, IL-1β, and tumour necrosis factor alpha (TNFα) (49). Shing and colleagues (46) conducted an *in vitro* experiment examining the influence of BC in stimulating cytokine production by peripheral blood mononuclear cells collected from resting healthy volunteers. Interestingly, BC significantly increased the production of interferon-γ, IL-10, and IL-2 by peripheral blood mononuclear cells, but inhibited lipopolysaccharide (LPS)-stimulated production of TNFα, IL-6 and IL-4 (46). These findings have significant implications regarding GI permeability during exercise that will be further discussed in the next section. Furthermore, the high concentration of Ig's within BC has provoked a number of investigations examining the association of BC intake with exercise-induced immunosuppression and the incidence of upper respiratory tract infections (3, 13, 15, 34) that is commonly reported following intense exercise (9). Preliminary findings suggest that BC intake in humans is associated with a reduction in upper respiratory tract infection symptoms (3, 34) and either an increase (13) or no change (45) in salivary IgA. This relationship remains inconsistent and requires further investigation, since salivary IgA has been suggested as the primary mechanism responsible for reducing the incidence of upper respiratory tract infections (3).

BOVINE COLOSTRUM SUPPLEMENTATION AND EXERCISE HEAT TOLERANCE

Supplementation with BC has been shown to improve exercise performance (18, 44). For example, five weeks of BC supplementation (10 g/day) in highly trained cyclists significantly increased performance during a 40 km time trial compared to placebo (44). In contrast, BC supplementation for eight weeks (60 g/day) in physically active males did not improve performance during an initial incremental running test to exhaustion, but was associated with a higher peak running speed during a subsequent run, compared to placebo, indicating a potential enhancement of recovery (5). During intense exercise, blood is distributed to the periphery and plasma volume is decreased, which limits the amount of blood flow to the GI tract, particularly in hot conditions (22, 41). As mentioned above, this compromises the integrity of the GI intestinal walls resulting in the leakage of LPS into circulation, characteristic of endotoxemia, which is believed to play a major role in the aetiology of heat stroke (24, 26). For example, circulating LPS concentrations have been shown to be increased in humans after experiencing heat stroke (2), in fatigued endurance athletes (4), and heat-stressed mammals (17). LPS is a cell-wall component of Gram-negative bacteria and a well-known inducer of the innate immune response. In circulation, LPS has the ability to initiate an inflammatory cascade through interaction with CD14 (LPS receptor) and cell surface receptors such as toll-like receptor 4 (e.g. located on macrophages/monocytes) (51). For example, endotoxemia reported in patients with heat stroke was accompanied by a significant increase in circulating concentrations of TNFα and IL-1α, with levels significantly reduced following post-cooling (2). The endotoxemia-induced production of cytokines accelerates heat storage and fatigue through the induction of fever-like symptoms, and may influence fatigue directly through interaction with the central nervous system or by impairing skeletal muscle intrinsic force-generating capacity (48). Nevertheless, the leakage of LPS into circulation substantially contributes to the development of heat stroke and fatigue during exercise in the heat, which could negatively impact physical performance (10, 14). Although the available data are scarce, agents that may reduce or prevent GI permeability, such as BC, form an attractive field of future work for ameliorating the effects of endotoxemia and, thus, reduce the impact of heat stress on physical performance.

A number of studies indicate that BC can contribute to GI tract maintenance by recruiting healthy cells and by stimulating the growth of epithelial cells, which line the entire length of the GI tract (30, 37). To assess the efficacy of BC supplementation on maintaining GI permeability during heat stress, Prosser and colleagues (39) supplemented rats with BC for seven days and assessed the transfer of chromium-labelled ethylenediaminetetraacetic acid (Cr-EDTA) from the gut to circulation while increasing their core temperature to 41.5°C. The transfer of Cr-EDTA to circulation was significantly less with BC supplementation compared to heat-stress alone, which increased Cr-EDTA transfer by 34-fold. The authors suggest the influence of BC on maintaining tight junctions in epithelial cells as a potential mechanism for preserving GI integrity (39). Improvements in GI permeability during passive heating following BC supplementation raises interesting questions regarding its influence during exercise heat stress, which has, to date, not been examined. To our knowledge, there is only study that has investigated the influence of BC supplementation on GI permeability during exercise to exhaustion (6). Buckley and colleagues supplemented healthy males with BC (60 g/day), whey protein, or control for eight weeks during exercise training (i.e. running three times per week); they reported a significant increase in intestinal permeability following BC supplementation only, compared to baseline, determined by the ratio of urinary lactulose and rhamnose excretion (6). The authors suggested that GI permeability after BC supplementation may be increased in a healthy adult gut or that BC increased the intestinal transport of macromolecules as it does in the neonatal gut (6). A closer inspection of the data, however, reveals that the BC group may have actually performed better during the post-supplementation trial compared to controls, a finding masked by a low sample size and statistical power. Thus, it is possible that the increase in gut permeability after BC supplementation may have actually occurred because of differences in exercise stress. Nevertheless, more research is required to determine the influence of BC supplementation on GI permeability during intense exercise, particularly during hot conditions, and to determine who would benefit from BC ingestion, as well as optimal BC dosage.

CONCLUDING REMARKS

The transfer of immune and growth factors via BC are essential for the survival of newborn mammals. Exploiting this condensed bioactive substance for the benefit of improving physical performance has received recent attention. The influence of BC supplementation on exercise performance in the heat warrants further study based on its potential to maintain GI permeability and thus, reduce LPS leakage into circulation and delay fatigue. Research in this area is still in its early stages and is only based on a few studies. Questions still remain regarding which exercise type/intensity and environmental conditions would necessitate BC supplementation, as well as the effects in different populations, and optimal timing and dosage strategies. Given that GI permeability is lessened during passive heat stress following BC supplementation supports the notion that the benefits of BC may be transferable to exercise and, even more, to exercise in hot environments. The implication of LPS-induced cytokine production during endotoxemia in causing fatigue during exercise in the heat is a matter of growing importance given the global increase in ambient temperatures that characterize current climate change (12).

REFERENCES

1. Blattler, U., Hammon, H.M., Morel, C., Philipona, C., Rauprich, A., Rome, V., Le Huerou-Luron, I., Guilloteau, P., and Blum, J.W., Feeding colostrum, its composition and feeding duration variably modify proliferation and morphology of the intestine and digestive enzyme activities of neonatal calves. *J Nutr.* 2001, **131**: 1256-1263.
2. Bouchama, A., Parhar, R.S., el-Yazigi, A., Sheth, K., and al-Sedairy, S., Endotoxemia and release of tumor necrosis factor and interleukin 1 alpha in acute heatstroke. *J Appl Physiol.* 1991, **70**: 2640-2644.
3. Brinkworth, G.D., and Buckley, J.D., Concentrated bovine colostrum protein supplementation reduces the incidence of self-reported symptoms of upper respiratory tract infection in adult males. *Eur J Nutr.* 2003, **42**: 228-232.
4. Brock-Utne, J.G., Gaffin, S.L., Wells, M.T., Gathiram, P., Sohar, E., James, M.F., Morrell, D.F., and Norman, R.J., Endotoxaemia in exhausted runners after a long-distance race. *S Afr Med J.* 1988, **73**: 533-536.
5. Buckley, J.D., Abbott, M.J., Brinkworth, G.D., and Whyte, P.B., Bovine colostrum supplementation during endurance running training improves recovery, but not performance. *J Sci Med Sport.* 2002, **5**: 65-79.
6. Buckley, J.D., Butler, R.N., Southcott, E., and Brinkworth, G.D., Bovine colostrum supplementation during running training increases intestinal permeability. *Nutrients*. 2009, **1**: 224-234.
7. Bush, L.J., and Staley, T.E., Absorption of colostral immunoglobulins in newborn calves. *J Dairy Sci.* 1980, **63**: 672-680.
8. Butler, J.E., The occurrence of immunoglobulin fragments, two types of lactoferrin and a lactoferrin-IgG2 complex in bovine colostral and milk whey. *Biochim Biophys Acta.* 1973, **295**: 341-351.
9. Carrillo, A.E., Murphy, R.J., and Cheung, S.S., Vitamin C supplementation and salivary immune function following exercise-heat stress. *Int J Sports Physiol Perform.* 2008, **3**: 516-530.
10. Cheung, S.S., and Sleivert, G.G., Multiple triggers for hyperthermic fatigue and exhaustion. *Exerc Sport Sci Rev.* 2004, **32**: 100-106.
11. Clausen, J.P., Effect of physical training on cardiovascular adjustments to exercise in man. *Physiol Rev.* 1977, **57**: 779-815.
12. Costello, A., Abbas, M., Allen, A., Ball, S., Bell, S., Bellamy, R., Friel, S., Groce, N., Johnson, A., Kett, M., Lee, M., Levy, C., Maslin,

M., McCoy, D., McGuire, B., Montgomery, H., Napier, D., Pagel, C., Patel, J., de Oliveira, J.A., Redclift, N., Rees, H., Rogger, D., Scott, J., Stephenson, J., Twigg, J., Wolff, J., and Patterson, C., Managing the health effects of climate change: Lancet and University College London Institute for Global Health Commission. *Lancet.* 2009, **373**: 1693-1733.

13. Crooks, C.V., Wall, C.R., Cross, M.L., and Rutherfurd-Markwick, K.J., The effect of bovine colostrum supplementation on salivary IgA in distance runners. *Int J Sport Nutr Exerc Metab.* 2006, **16**: 47-64.

14. Davis, J.M., and Bailey, S.P., Possible mechanisms of central nervous system fatigue during exercise. *Med Sci Sports Exerc.* 1997, **29**: 45-57.

15. Davison, G., and Diment, B.C., Bovine colostrum supplementation attenuates the decrease of salivary lysozyme and enhances the recovery of neutrophil function after prolonged exercise. *Br J Nutr.* 2010, **103**: 1425-1432.

16. Godden, S., Colostrum management for dairy calves. *Vet Clin North Am Food Anim Pract.* 2008, **24**: 19-39.

17. Hall, D.M., Buettner, G.R., Oberley, L.W., Xu, L., Matthes, R.D., and Gisolfi, C.V., Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. *Am J Physiol Heart Circ Physiol.* 2001, **280**: H509-521.

18. Hofman, Z., Smeets, R., Verlaan, G., Lugt, R., and Verstappen, P.A., The effect of bovine colostrum supplementation on exercise performance in elite field hockey players. *Int J Sport Nutr Exerc Metab.* 2002, **12**: 461-469.

19. Jeukendrup, A.E., Vet-Joop, K., Sturk, A., Stegen, J.H., Senden, J., Saris, W.H., and Wagenmakers, A.J., Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. *Clin Sci (Lond).* 2000, **98**: 47-55.

20. Kim, J.W., Jeon, W.K., Yun, J.W., Park, D.I., Cho, Y.K., Sung, I.K., Sohn, C.I., Kim, B.I., Yeom, J.S., Park, H.S., Kim, E.J., and Shin, M.S., Protective effects of bovine colostrum on non-steroidal anti-inflammatory drug induced intestinal damage in rats. *Asia Pac J Clin Nutr.* 2005, **14**: 103-107.

21. Koutedakis, Y., Budgett, R., and Faulmann, L., Rest in underperforming elite competitors. *Br J Sports Med.* 1990, **24**: 248-252.

22. Lambert, G.P., Role of gastrointestinal permeability in exertional heatstroke. *Exerc Sport Sci Rev.* 2004, **32**: 185-190.

23. Lambert, G.P., Broussard, L.J., Mason, B.L., Mauermann, W.J., and Gisolfi, C.V., Gastrointestinal permeability during exercise: effects of aspirin and energy-containing beverages. *J Appl Physiol.* 2001, **90**: 2075-2080.

24. Lambert, G.P., Gisolfi, C.V., Berg, D.J., Moseley, P.L., Oberley, L.W., and Kregel, K.C., Selected contribution: Hyperthermia-induced intestinal permeability and the role of oxidative and nitrosative stress. *J Appl Physiol.* 2002, **92**: 1750-1761; discussion 1749.

25. Larson, B.L., Heary, H.L., Jr., and Devery, J.E., Immunoglobulin production and transport by the mammary gland. *J Dairy Sci.* 1980, **63**: 665-671.

26. Lin, X.J., Li, Y.J., Li, Z.L., Zou, F., and Lin, M.T., Pre-existing lipopolysaccharide may increase the risk of heatstroke in rats. *Am J Med Sci.* 2009, **337**: 265-270.

27. Marchbank, T., Davison, G., Oakes, J.R., Ghatei, M.A., Patterson, M., Moyer, M.P., and Playford, R.J., The nutriceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes. *Am J Physiol Gastrointest Liver Physiol.* 2011, **300**: G477-484.

28. Mir, R., Singh, N., Vikram, G., Kumar, R.P., Sinha, M., Bhushan, A., Kaur, P., Srinivasan, A., Sharma, S., and Singh, T.P., The structural basis for the prevention of nonsteroidal antiinflammatory drug-induced gastrointestinal tract damage by the C-lobe of bovine colostrum lactoferrin. *Biophys J.* 2009, **97**: 3178-3186.

29. Moore, M., Tyler, J.W., Chigerwe, M., Dawes, M.E., and Middleton, J.R., Effect of delayed colostrum collection on colostral IgG concentration in dairy cows. *J Am Vet Med Assoc.* 2005, **226**: 1375-1377.

30. Murphy, M.S., Growth factors and the gastrointestinal tract. *Nutrition.* 1998, **14**: 771-774.

31. Ontsouka, C.E., Sauter, S.N., Blum, J.W., and Hammon, H.M., Effects of colostrum feeding and dexamethasone treatment on mRNA levels of insulin-like growth factors (IGF)-I and -II, IGF binding proteins-2 and -3, and on receptors for growth hormone, IGF-I, IGF-II, and insulin in the gastrointestinal tract of neonatal calves. *Domest Anim Endocrinol.* 2004, **26**: 155-175.

32. Pakkanen, R., and Aalto, J., Growth factors and antimicrobial factors of bovine colostrum. *Int Dairy J.* 1973, **7**: 285-297.

33. Parry-Billings, M., Budgett, R., Koutedakis, Y., Blomstrand, E., Brooks, S., Williams, C., Calder, P.C., Pilling, S., Baigrie, R., and Newsholme, E.A., Plasma amino acid concentrations in the overtraining syndrome: possible effects on the immune system. *Med Sci Sports Exerc.* 1992, **24**: 1353-1358.

34. Patel, K., and Rana, R., Pedimune in recurrent respiratory infection and diarrhoea--the Indian experience--the pride study. *Indian J Pediatr.* 2006, **73**: 585-591.

35. Playford, R.J., Floyd, D.N., Macdonald, C.E., Calnan, D.P., Adenekan, R.O., Johnson, W., Goodlad, R.A., and Marchbank, T., Bovine colostrum is a health food supplement which prevents NSAID induced gut damage. *Gut.* 1999, **44**: 653-658.

36. Playford, R.J., MacDonald, C.E., Calnan, D.P., Floyd, D.N., Podas, T., Johnson, W., Wicks, A.C., Bashir, O., and Marchbank, T., Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. *Clin Sci (Lond).* 2001, **100**: 627-633.

37. Playford, R.J., Macdonald, C.E., and Johnson, W.S., Colostrum and milk-derived peptide growth factors for the treatment of gastrointestinal disorders. *Am J Clin Nutr.* 2000, **72**: 5-14.

38. Playford, R.J., Woodman, A.C., Clark, P., Watanapa, P., Vesey, D., Deprez, P.H., Williamson, R.C., and Calam, J., Effect of luminal growth factor preservation on intestinal growth. *Lancet.* 1993, **341**: 843-848.

39. Prosser, C., Stelwagen, K., Cummins, R., Guerin, P., Gill, N., and Milne, C., Reduction in heat-induced gastrointestinal hyperpermeability in rats by bovine colostrum and goat milk powders. *J Appl Physiol.* 2004, **96**: 650-654.

40. Rowell, L.B., Murray, J.A., Brengelmann, G.L., and Kraning, K.K., 2nd. Human cardiovascular adjustments to rapid changes in skin temperature during exercise. *Circ Res.* 1969, **24**: 711-724.

41. Sakurada, S., and Hales, J.R., A role for gastrointestinal endotoxins in enhancement of heat tolerance by physical fitness. *J Appl Physiol.* 1998, **84**: 207-214.

42. Sharp, N.C., and Koutedakis, Y., Sport and the overtraining syndrome: immunological aspects. *Br Med Bull.* 1992, **48**: 518-533.

43. Shing, C.M., Hunter, D.C., and Stevenson, L.M., Bovine colostrum supplementation and exercise performance: potential mechanisms. *Sports Med.* 2009, **39**: 1033-1054.

44. Shing, C.M., Jenkins, D.G., Stevenson, L., and Coombes, J.S., The influence of bovine colostrum supplementation on exercise performance in highly trained cyclists. *Br J Sports Med.* 2006, **40**: 797-801.

45. Shing, C.M., Peake, J., Suzuki, K., Okutsu, M., Pereira, R., Stevenson, L., Jenkins, D.G., and Coombes, J.S., Effects of bovine colostrum supplementation on immune variables in highly trained cyclists. *J Appl Physiol.* 2007, **102**: 1113-1122.

46. Shing, C.M., Peake, J.M., Suzuki, K., Jenkins, D.G., and Coombes, J.S., Bovine colostrum modulates cytokine production in human peripheral blood mononuclear cells stimulated with lipopolysaccharide and phytohemagglutinin. *J Interferon Cytokine Res.* 2009, **29**: 37-44.

47. Stelwagen, K., Carpenter, E., Haigh, B., Hodgkinson, A., and Wheeler, T.T., Immune components of bovine colostrum and milk. *J Anim Sci.* 2009, **87**: 3-9.

48. Supinski, G., Nethery, D., Nosek, T.M., Callahan, L.A., Stofan, D., and DiMarco, A., Endotoxin administration alters the force vs. pCa relationship of skeletal muscle fibers. *Am J Physiol Regul Integr Comp Physiol.* 2000, **278**: R891-896.

49. Thapa, B.R., Health factors in colostrum. *Indian J Pediatr.* 2005, **72**: 579-581.

50. Thapa, B.R., Therapeutic potentials of bovine colostrums. *Indian J Pediatr.* 2005, **72**: 849-852.

51. Tsan, M.F., and Gao, B., Endogenous ligands of Toll-like receptors. *J Leukoc Biol.* 2004, **76**: 514-519.

52. Van Leeuwen, P.A., Boermeester, M.A., Houdijk, A.P., Ferwerda, C.C., Cuesta, M.A., Meyer, S., and Wesdorp, R.I., Clinical significance of translocation. *Gut.* 1994, **35**: S28-34.

53. Wong, W.M., and Wright, N.A., Epidermal growth factor, epidermal growth factor receptors, intestinal growth, and adaptation. *JPEN J Parenter Enteral Nutr.* 1999, **23**: S83-88.

54. Yamanaka, H., Hagiwara, K., Kirisawa, R., and Iwai, H., Proinflammatory cytokines in bovine colostrum potentiate the mitogenic response of peripheral blood mononuclear cells from newborn calves through IL-2 and CD25 expression. *Microbiol Immunol.* 2003, **47**: 461-468.