Review

Bovine Colostrum – The Promising Nutraceutical

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Abstract

Alexieva B., Markova Tz., Nikolova E. (2004): **Bovine colostrum – the promising nutraceutical**. Czech J. Food Sci., **22**: 73–79.

Colostrum is the first milk produced after birth and is particularly rich in immunoglobulins, antimicrobial peptides, and growth factors. It is important for the nutrition, growth, and development of newborn infants and contributes to the immunologic defence of neonates. Recent studies suggest that bovine colostrum or some of its constituents may be useful for the prevention and, to some extent, for the treatment of various infectious diseases. A variety of colostral based preparations have been used as feed supplements or colostrum substitutes for neonate calves and pigs. Numerous recent studies suggest that oral administration of bovine colostrum preparations may contribute to human health care both as part of health promoting diet and as an alternative or a supplement to the medical treatment of specified human diseases.

Keywords: diet supplement; nutrient; colostral immunoglobulins; growth factors; human health

Colostrum is the first lacteal secretion in all mammals immediately following the birth. It is only secreted during the first few days after parturation and is highly nutritious. It contains immunoglobulins, growth factors, vitamins, minerals, enzymes, amino acids and other substances designed to provide the newborn with the ability to face the invasion by microorganisms and environmental toxins.

Colostral immunoglobulins provide the major antimicrobial protection against infections and confer a passive immunity on the newborn until its own immune system matures. They bind to invading organisms and activate specific actions that help to prevent infection and to rid the body of pathogenic microorganisms. They function in cell killing, inflammation, and prevention of bacterial and viral attachment.

Mammals reveal certain differences in immunoglobulin transfer pathways. In humans and apes, mother passively immunises her offspring in uterus by the passage of antibodies through the placenta. In animals, where maternal antibodies do not pass the placental barrier (horses, cattle, pigs, and sheep), the newborn is passively immunised immediately after birth via colostrum. Such animals are born virtually without any immunity and thus their immune system depends on the ingested maternal colostrum which contains a lot of immune factors. In a newborn calf, the immunoglobulins are absorbed from the colostrum into the circulation within 24–36 h after birth via a non-selective macromolecular transport system (Mc Fadden *et al*. 1997).

Bovine serum and lacteal secretions contain three major classes of immunoglobulins: IgG, IgM and IgA. The first colostrum contains very high concentrations of immunoglobulins (40–200 g/l). In bovine colostrum they constitute up to 70–80% of the total protein content whereas in mature milk their content is only 1–2%. Over 90% of bovine colostral immunoglobulins are of IgG class and the mean concentration at the first milking after birth is approximately 60 g/l. IgG concentration falls sharply to aproximately 1 g/l at the 12th milking, reaching 0.5 g/l in mature milk (Levieux & Ollier 1999). IgA content varies between 1 and 6 g/l and that of IgM varies between 3 and 5 g/l in cow colostrum as compared with 0.05 and 0.04 g/l in mature milk, respectively (Lilius & Marnila 2001).

In human colostrum and mature milk the IgA class is dominant and it constitutes over 90% of all immunoglobulins. The average IgA content in colostrum and mature milk is approximately 11 g/l and 0.5 g/l, respectively. The average concentration of IgG in colostrum is 0.4 g/l, and that of IgM 0.3 g/l, respectively, but only 0.04 and 0.03 g/l, respectively, in human mature milk (Prentise 1995).

Together with the antibodies absorbed from colostrum after birth, the complement system plays a crucial role in the passive immunisation of the newborn calf (Korhonen *et al*. 2000a). It plays a major role in the host defence mechanisms against microorganisms as it is involved both in specific and non-specific immunity. The killing of microorganisms, clearing of immune complexes, and induction and enhancement of the antibody responses are the major biological functions of complement. The complete complement system can be found in bovine colostrum and components of the system are present in milk. Several studies have demonstrated the occurrence of haemolytic or bactericidal complement activity in bovine colostrum (Brock *et al*. 1975; Eckblad *et al*. 1981; Korhonen *et al*. 1995).

The progress in understanding the underlying mechanisms of immunity has provoked an increasing interest in the development of immune milk preparations for the prevention or treatment of microbial and viral infections in animals and humans. Basically, the approaches to the development of Ig-based preparations are either the isolation and/or concentration of Igs occurring naturally in colostrum or milk, or the hyperimmunisation of pregnant cows during the "dry" period with antigens from pathogens in order to raise specific antibodies in the mammary secretions.

Immune colostrum products are preparations made of such hyperimmune colostrum or antibodies enriched from it. They can be used as feed supplements or colostrum substitutes to give effective protection against different enteric diseases in calves and pigs (Korhonen *et al*. 2000b). Colostral immunoglobulin supplements designed for farm animals are commercially available in many countries.

A number of clinical studies are currently in progress with the aim to evaluate the efficiency of immune colostrum in the prevention and treatment of various human infections, including those caused by antibiotic resistant bacteria. Immunoglobulins of bovine milk ingested by humans are degraded by pepsin and the intestinal proteases, trypsin, chymotrypsin, carboxypeptidase, and elastase into $F(ab)_2$, Fab and Fc fragments; the secretory component of IgA more resistant to proteolysis than other classes of immunoglobulins (Reilly *et al*. 1997). The $F(ab)_2$, and Fab fragments retain some of the neutralising activity of the intact antibody. Bovine immunoglobulins have been detected in the faeces of human infants fed with bovine immune milk, and in some studies with human volunteers (Roos *et al*. 1995). Approximately half of bovine IgG has been shown to remain immunologically active in ileum of adult humans (Warny *et al*. 1999).

Oral administration of bovine colostrum based immune products containing high titers of specific antibodies can provide effective protection and to some extent may also be of therapeutic value against various infectious diseases in humans. Good results have been obtained with products targeted against rotavirus (Davidson *et al*. 1989; Mitra *et al*. 1995; Sarker *et al*. 1998), *Shigella flexnery* (Tacket *et al*. 1992), *Escherichia coli* (Freedman *et al*. 1998; Huppertz *et al*. 1999), *Streptococcus mutans* (Loimaranta *et al*. 1998, 1999), *Cryptosporidium parvum* (Greenberg & Cello 1996; Okhuysen *et al*. 1998), and *Helicobacter pylori* (Tarpila *et al*. 1995; Oona *et al*. 1997). Promissing results have been reported in the treatment of patients with autoimmune deficiency syndrome (AIDS) (Stephan *et al*. 1990; Rump *et al*. 1992). Some successful attempts have been made to use immune colostrum to balance gastrointestinal microbial flora (Zeitlin *et al*. 2000). Immune colostral products are promising examples of health promoting functional foods or nutraceuticals.

A great deal of information is available on the biological function of the components from bovine colostrum. Antimicrobial and antiviral activity of colostrum is due not only to immunoglobulins and the complement system. The iron binding glycoprotein lactoferrin is responsible for the elimination of endotoxins and takes part in the host defence and the modulation of iron metabolism (Selfert *et al*. 2000; Steijns & Van Hooijdonk 2000). Biological activity of bovine κ-caseino glycomacropeptide (GMP) has received much attention in recent years. Research has been focused on the ability of GMP to bind *Cholera* and *E. coli* enterotoxins, inhibit bacterial adhesion, suppress gastric secretions, promote bifidobacterial growth, and modulate immune system responses (Brody 2000). Oligosaccharides and glycoconjugates are some of the most important biological components in colostrum. Their primary role seems to reside in providing protection against pathogens by acting as competitive inhibitors on the binding sites on the epithelial surfaces of the intestine. Evidence is also available to support the role of some of these components as growth promotors for genera of beneficial microflora in the colon. The chemical structure of the oligosaccharides and many of the glycoconjugates from bovine milk are similar to those in human milk. It is likely that bovine oligosaccharides and glycoconjugates can be useful in the milk products as bioactive components in human nutrition (Gopal & Gill 2000). Nucleotides, nucleosides and nucleobases belong to the non-protein nitrogen (NPN) fraction of milk. They are used by the body as exogenous trophochemical sources and can be important for optimal metabolic functions. They not only act as metabolites, but are also involved as bioactive substances in the regulation of the body functions. There is evidence that NPN affects the immune modulation by enhancing the antibody responses of infants, contributes to the iron absorption in the gut, and also influences desaturation and elongation rates in fatty acid synthesis (Schlimme *et al*. 2000).

It was confirmed that two colostral components (MW 19000 D and 31000 D) in serum transferred from colostrum are present in cerebrospinal fluid (CSF). The component of MW 19000 was identified as β-lactoglobulin. Lactoferrin was also detected in the CSF via serum. These results indicate that some components of colostrum can be transported into the CFS via the serum, suggesting the possibility of modification of the immature brain function by colostral suckling (Harada *et al*. 1999).

Colostrum and milk contain many factors that can influence the cell growth, differentiation, and function. Several nonpeptide constituents of colostrum, when added to cells *in vitro* or when infused into animal models, have resulted in increased cell proliferation. These factors include glutamine, polyamines, and nucleotides. It is debatable whether these factors should be considered as growth factors per se because the increased proliferation is not mediated by the classic receptor-ligand secondary messenger system (Playford 1995).

Colostrum is also a rich source of natural growth factors in high concentrations. These small bioactive molecules promote growth and maturation of various cell types and tissues. Major peptide growth factor constituents of colostrum and milk are: epidermal growth factor (EGF), transforming growth factor α and β (TGF-α and TGF-β), insulin-like growth factors I and II (IGF I and IGF II), platelet – derived growth factor (PDGF), bovine colostral growth factor (BCGF), and several other peptides whose structure and function are less clearly defined.

EGF is produced by the salivary glands and the Brunners glands of the duodenum in adults and probably acts as "luminal surveilance peptide" readily available to stimulate the repair process at sites of injury (Playford 1995). It also may play a role in preventing bacterial translocation and in stimulating the gut growth in suckling neonates (Okuyama *et al*. 1998). In contrast to EGF, TGF-α is produced within the mucosa throughout the gastrointestinal tract. It stimulates gastrointestinal growth and repair, inhibits acid secretion, stimulates mucosal restitution after injury, and increases gastric mucin concentrations. TGF-β has many diverse functions – it is a potent chemoattractant for neutrophils and stimulates epithelial cell migration at wound sites. It is a key player in stimulating restitution, the early phase of the repair prosess during which surviving cells from the edge of a wound migrate over the denuded area to reestablish epithelial continuity (Playford *et al*. 2000). IGF I and IGF II promote cell proliferation and differentiation (Daughaday & Rotwein 1989). Bovine colostrum contains much higher concentrations of them than does human colostrum and they are relatively stable under both heat and acidic conditions. They therefore maintain their biological activity on both commercial milk processing and under gastric acid conditions. IGF I and IGF II are known as anabolic agents. They are of special interest as they mediate many of growth hormone effects *in vivo* and stimulate the general tissue growth via direct effects on

IGF receptors (Hossner & Yemm 2000). PDGF is an acid-stable molecule that was originally identified in platelets but is also syntesised and secreted by macrophages. It is a potent mitogen for fibroblasts and arterial smooth muscle cells and facilitates ulcer healing when administered orally to animals (Szabo & Sandor 1996).

Growth factors not only stimulate normal growth and development, but also help regenerate and accelerate the repair of injured skin, mucosa, muscle, bone, cartilage, and nerve tissues. They also help build lean muscle and have been shown to have a positive effect on athletic performance (Antonio *et al*. 2001). It appears that bovine colostrum supplement may increase the serum insulin-like growth factor-1 (IGF-1) concentration in athletes during strength and speed training (Mero *et al*. 1997). Recent studies have suggested an important role for the growth factors in promoting wound healing. It is postulated that IGF-1 is an important mitogen for wound healing in the human skin explant model. Bovine colostrum has the growth factor activity for stimulating DNA synthesis. The medium based or the ultrafiltrate fraction of bovine colostrum and adult bovine serum can be used successfully as a fetal bovine serum (FBS) substitute in the culture of several anchorage-dependent and independent cell lines (Viander *et al*. 1996). Non-steroidal anti-inflamatory drugs (NSAIDs) are effective for arthritis but cause gastrointestinal injury. Using indomethacin restraint rat model of gastric damage, indomethacin mouse model of small intestine injury, and an *in vitro* model of wound repair, it was concluded that bovine colostrum could provide a novel inexpensive approach for the prevention and treatment of injurious effects of NSAIDs on the gut and may also be of value for the treatment of other ulcerative conditions of the bowel (Playford 1995; Playford *et al*. 1999). Studies on volunteers and patients taking NSAIDs for clinical reasons provide evidence that defatted colostrum reduces the rise in gut permeability (a non-invasive marker of intestinal injury) (Playford *et al*. 2001).

Current regimens for the treatment of cancers require the patients to take much higher doses of chemotherapeutic agents than were used previously. As a result, adverse toxic effects on the bone marrow and gastrointestinal tract are factors limiting the dose or duration of the treatment. There exists evidence that EGF enhances the repair of rat intestinal mucosa damaged by methotrexate (Hirano *et al*. 1994), and that TGF-β ameliorates chemotherapy-induced mucositis (Soins *et al*. 1994).

It is likely, however, that over the next few years, additional novel growth factors with clinical potential will be identified in colostrum and milk.

Colostrum contains high levels of cytokines (IL-1β, IL-6, IL-10, TNF-α, INF-γ, IL-1receptor antagonist) that could be produced in and secreted by the mammary gland and that have immunomodulatory properties (Hagiwara *et al.* 2000). It is likely that in newborn animals and infants, these factors play an important role in modulating immunologic development, working in combination with the ingested maternal immunoglobulins and the nonspecific antibacterial components such as lactoperoxidase in colostrum.

The effect of bovine colostrum on phagocytic activity on latex particles by peripheral blood polymorphonuclear leucocytes has been investigated. The results indicate that bovine colostrum strongly activates phagocytosis, thus suggesting the concernment with the development of nonspecific immune system in newborns (Sugisawa *et al*. 2001).

Big cosmetic companies have shown an increasing interest in colostral-based nutriceutical creams which help regenerate and accelerate the repair of aged skin.

The world-wide trend towards the development of health-promoting functional foods offers interesting opportunities for applications which contain specific antibody ingredients derived from immunised cows. It is anticipated that immune colostral or milk-based preparations may have remarkable potential to contribute to human health care, both as part of a health – promoting diet and as an alternative or a supplement to the medical treatment of specified human diseases.

Cow's colostrum and milk contain virtually all compounds of bovine cellular and humoral immune defence. They are ideal sources of these defence molecules for industrial production because of their ready availability and safety as compared for example with blood derived analogues. The main limitation of milk antibodies in human use is that they are derived from a foreign species and can thus be used only against oral and gastrointestinal pathogens or for topical applications. In order to overcome this limitation, it may be possible in the future to produce human antibodies and complement proteins in transgenic cows.

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Received for publication January 13, 2003
Accepted February 18, 2004

Souhrn

Alexieva B., Markova Tz., Nikolova E. (2004): **Hovězí mlezivo – slibné nutraceutikum.** Czech J. Food Sci., **22**: 73–79.

Mlezivo je první mléko produkované po porodu a je zvláště bohaté na imunoglobuliny, antimikrobiální peptidy a na růstové faktory. Je důležité pro výživu, růst a vývoj novorozených mláďat a přispívá k imunologické obraně novorozenců. Podle nedávných studií může být bovinní mlezivo a některé jeho složky užitečné pro prevenci některých infekčních nemocí a do určité míry i pro jejich léčbu. Řada preparátů, založených na mlezivu, byla použita jako potravinové doplňky nebo náhražky mleziva pro novorozená telata a selata. Podle nedávných studií se dá předpokládat, že orální podávání preparátů z hovězího mleziva může přispívat k humánní zdravotní péči jako součást zdraví prospěšných diet i jako alternativa či doplněk medicínské léčby specifických lidských nemocí.

Klíčová slova: potravinové doplňky; nutrienty; imunoglobuliny mleziva; růstové faktory; lidské zdraví

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