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Review Article

# Pharmacological activities and potential use of bovine colostrum for peptide-based radiopharmaceuticals: A review

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## Abstract

Bovine colostrum (BC) is the initial milk produced by cows after giving birth. It has been used to treat human diseases, such as infections, inflammations, and cancers. Accumulating evidence suggests that bovine lactoferrin and bovine antibodies seem to be the most important bioactive constituents in BC. Thus, BC has also been reviewed for its potential to deliver short-term protection against coronavirus disease 2019 (COVID-19). In addition, it can potentially be explored as a precursor for peptide-based radiopharmaceuticals. To date, several bioactive peptides have been isolated from BC, including casocidin-1, casecidin 15 and 17, isracidin, caseicin A, B, and C. Like other peptides, bioactive peptides derived from BC could be used as a valuable precursor for radiopharmaceuticals either for diagnosis or therapy purposes. This review provides bovine colostrum's biological activities and a perspective on the potential use of peptides from BC for developing radiopharmaceuticals in nuclear medicine.

## Keywords

Antibodies, biological activities, bovine colostrum, peptides, radiopharmaceuticals

## Introduction

Bovine colostrum (BC) is the milky fluid secreted by cows in the first few days after giving birth that has important potential to promote beneficial effects through the improvement of immunological functions. In dairy cows, bovine antibodies are actively transported from the mammary epithelial cells to the mammary gland by receptor-mediated mechanisms, and are present in high concentration in colostrum (Weiner et al. 1999; Hurley and Theil 2011). BC contains a high concentration of nutrient and bioactive components, such as carbohydrates, proteins, fat, immunoglobulins, vitamins, minerals, natural antimicrobial agents (lactoferrin, lysozyme, and lactoperoxidase), and growth factors (Kelly 2003; Silva et al. 2019). Several bioactive compounds in BC will be declining over the subsequent three days, suggesting that colostrum secreted on the first day of calving is more critical than that secreted in the later days of lactation. Thus, BC not only provides nutrition but also offers passive immunity for the protection of newborns against various pathogens, boosts the maturity of the immune system, promotes growth, provides maturation, and enhances damaged tissue healing (Shing et al. 2009; França-Botelho 2019; Menchetti et al. 2020).

As crucial as for calves, BC is also one of the valuable components with rich health benefits for humans and has been used as a dietary supplement (Glowka et al. 2020). It is noteworthy that BC possesses unique nutritional and



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biological activities that can be species-specific or across species, and therefore may also benefit a specific group of humans (Rathe et al. 2014). Interestingly, the bioactive composition of colostrum is highly variable, affecting by many factors, including breed, health status, parity, nutrition, dry period duration, and time post-partum (Kelly 2003; McGrath et al. 2015). Accordingly, it is expected that immunological activities expressed by specific BC products cannot necessarily be presumed to be a result that will be yielded by all BC. The main immunological component found in BC is immunoglobulin G (IgG), followed by immunoglobulin A (IgA) and immunoglobulin M (IgM). Immunoglobulins, also called antibodies, have been acknowledged for many years as the essential biomolecules which display many biological roles, in particular as immunological protection against microbial pathogens and toxins (Ulfman et al. 2018).

The biological effect of BC immunoglobulins on human health, especially for immune functions, has been widely studied, and continues to be an area of interest. Accumulating evidence suggests that BC IgG could bind to some variety of infectious bacteria, viruses, and allergens (Ulfman et al. 2018). In vitro study revealed that polyvalent immunoglobulins derived from BC with the addition of vitamin D3 showed beneficial effects on cytokine levels and systemic inflammation in colorectal cancer patients by suppressing the level of pro-inflammatory substances and promoting the production of anti-inflammatory cytokines, suggesting that these substances deserve further investigation as a novel treatment in cancers and immune-related disorders (Gasser et al. 2018) Studies also revealed that BC could potentially be used against severe acute respiratory syndrome (SARS), avian influenza, and other human respiratory infections (Hurley and Theil 2011). More recently, bioactive components in BC either isolated from vaccinated and unvaccinated cows have been reviewed for their potential as a short-term protection agent against SARS-CoV-2 infection (COVID-19) in humans and could be used as an alternative treatment until a vaccine becomes commercially available (Jawhara 2020; Mann and Ndung'u 2020).

Prior to discovering antibiotics, BC has been employed to cure numerous ailments, including bacteria-associated infections and physical illness linked with immunity (Xu et al. 2014). Additionally, many studies revealed that BC has participated in multiple physiological and protective effects in cancer and inflammation. These properties of BC make it possible to be used as an innovative therapeutic strategy in various diseases. For example, the effect of orally administrated bovine lactoferrin (bLf) has been shown in many studies, and seems to have pharmacological roles in reducing infection and inflammation, and prevent carcinogenesis (Tomita et al. 2009). In this review, we describe BC's most important beneficial activities as anti-inflammatory, anticancer, and anti-infective agents, trying to identify its potential use for the development of peptide-based radiopharmaceuticals in the future. Systematic literature studies were carried out using the following databases: Scopus, ScienceDirect, Medline, PubMed, and Google Scholar. The following keywords and their combination were used: bovine colostrum, cow's milk, immunoglobulins, antibodies, antiviral, antibacterial, anti-inflammatory, anticancer, radiolabelling, radionuclides, peptides, and radiopharmaceuticals.

## Anti-infective activities of BC

To combat infectious diseases, several antimicrobial compounds have been discovered so far (Upadhyay and Mishra 2017). Studies suggest that bioactive compounds in BC may not only possess local effects but also contribute to immunological networks, resulting in systemic outcomes after contact with the gut mucosa (Rathe et al. 2014). Bovine immunoglobulin colostrum that interacts with pathogenic agents could prevent infection, reduce gastrointestinal inflammation, inhibits bacteria growth, and enhances gastrointestinal barrier function in in vitro experiments (Ulfman et al. 2018). BLf seems to be the most crucial compound shown bacteriostatic and bactericidal activities in both preclinical and clinical studies. In general, the anti-infective role of bLf is due to two distinct mechanisms; binding to free iron at the infection sites, thus preventing microbial access to the essential substrate, and rupture the cell membrane of pathogens (Superti 2020).

A study by Anand and colleagues demonstrated that bLf could interact with parasite-host cells, such as red blood cells and macrophages in specific mechanisms depending on the level of iron saturation of lactoferrin. The authors revealed that incubation of iron saturated lactoferrin with bLf increases the phagocytic activity, production of reactive oxygen species, and Toll-like receptor expression (Anand et al. 2015). Moreover, a clinical study by Hu et al. revealed that bovine antibody-based oral immunotherapy has significant activity in controlling the *Helicobacter pylori* infection. After 28 days of treatment with the bovine antibody, thirteen patients became negative from thirty antibody-treated subjects as indicated by the C-14 urea breath test (Hu et al. 2015).

It was found that skimmed and concentrated late bovine colostrum that contains a high concentration of IgG exhibits anti-human rotavirus (HRV) activity in in vitro model, and therefore may be potentially used as a natural treatment, especially in immunocompromised subjects, such as children and the elderly (Inagaki et al. 2013). Further, Bojsen and co-workers showed that the addition of bovine macromolecular whey protein (MMWP) could reduce infection stimulated by four rotavirus strains (human (Wa), bovine (RF), porcine (YM), and simian (RRV)) in two human intestinal cell lines (FHs 74 Int and Caco-2) (Bojsen A et al. 2007). Another study by Gunaydin and colleagues revealed that a mixture of hyperimmune BC (HBC) and an engineered probiotic strain of *Lactobacillus* (*L. rhamnosus* GG) was effective in reducing the duration of diarrhea in a rotavirus infection mouse model than HBC alone (Gunaydin et al. 2014).

## Anti-inflammatory activities of BC

Some reports show that bLf can exert anti-inflammatory effects in numerous preclinical and clinical studies (Superti 2020). The anti-inflammatory activity of BC is associated with the immunoregulation of cytokines substances, such as interleukins (IL-1β, IL-2, IL-6, IL-17), tumour necrosis factor-α (TNF-α), interferon (IFN)-γ, and other non-antimicrobial compounds. Some studies have shown that BC may also be beneficial to maintain gut homeostatic and prevent inflammation in the gastrointestinal disorder subjects (Rathe et al. 2014). For instance, BC can reduce the level of interleukin (IL)-8 when Caco-2 and HT29 cells were treated with TNF-α (Chae et al. 2017). It also exhibits good pharmacological activities by modulating Toll-like receptor 4 (TLR4), microbiota, and pro-inflammatory cytokines in a 2,4,6-trinitrobenzene sulfonic acid (TNBS) animal model of induced colitis (Menchetti et al. 2020).

In combination with glutamine, BC demonstrates superior activity in reducing the non-steroidal anti-inflammatory drug (NSAID)-induced intestinal injury and bacterial translocation in animal models compared to the administration of BC or glutamine alone (Kim et al. 2005). Recent studies show that BC can reduce natural killer (NK) cell and monocyte actions and lymphoproliferative reactions to lipopolysaccharide (LPS) inducement (Xu et al. 2014), stimulates the release of IFN- γ, IL-10, and IL-2 in human peripheral blood mononuclear cells induced with LPS and phytohemagglutinin (Shing et al. 2009), prevents intestinal epithelial cells inflammation by inhibiting the NF-κB pathway (An et al. 2009), and reduces rheumatoid arthritis symptoms in a mouse model of collagen-induced arthritis (Hung et al. 2018). Orally administrated bLf seems to be an effective method for systemic immune modulation by providing an initial role on the intestinal immune system, followed by the secondary effect in promoting systemic immunity. Studies reveal that oral administration of bLf could promote IL-8 production in intestinal epithelial cells and enhances $CD4^+$, $CD8^+$, and NK cells expression in the intestinal mucosa. Additionally, it was observed that bLf could increase the number of immune cells in the lymph nodes and spleen, and facilitate the synthesis of Th-1 type cytokines (IP-12 and IFN-γ), which might be important to halt inflammation (Yamauchi et al. 2006).

## Anticancer activities of BC

Cancer is one of the significant public health concerns in global societies with high unmet medical needs (Wongso et al. 2013; Nugraha et al. 2020). The typical treatment strategies for cancer consist of chemotherapy, surgery, radiotherapy, bone marrow transplants, or combination therapies between those treatments. However, these strategies possess some limitations and side effects, for example, treatment with chemical drugs could cause vital organ toxicity and drug resistance, and radiotherapy results in indirect damage to surrounding tissues as a consequence of radiation exposure, whereas surgery may sometimes lead to tumour recurrence due to incomplete resection of cancerous cells (Bagwe-Parab et al. 2020; Upadhayay et al. 2020). Thus, there is a need for cost-effective, safe novel therapies, and more effective drugs with minimum side effects to provide better treatment to cancer patients (Vadlakonda et al. 2017). The use of protein components from bovine milk as natural compounds for cancer prevention and treatment is currently a promising field of research, as indicated by some encouraging results (Bagwe-Parab et al. 2020).

BC contains two significant families of protein, namely caseins and whey proteins. Lactoferrin, a globular glycoprotein with a molecular mass of approximately 80 kDa is one of the bioactive substances in caseins, and has been investigated for its anti-inflammatory, antioxidant, and anticancer properties (Pepe et al. 2013). In the past several years, scientific evidence has overwhelmingly shown that bLf exhibits different anticancer activities in multiple preclinical and clinical studies. The anticancer activities of bLf are probably due to the numerous cellular mechanisms, such as amelioration of immune activity, regulation of the carcinogenic enzymes, inhibition of angiogenesis, and induction of apoptosis (Superti 2020). In a study by Zhang et al., it was found that bLf could significantly inhibit breast cancer cells (MCF-7, T-47D, Hs578T, and MDA-MB-231) growth after 48 hours of treatment (Zhang et al. 2015). Similarly, the effect of bLf on cancer was demonstrated by Najmafshar and colleagues. In this study, they revealed that the immobilization of bLf onto graphene oxide increases anticancer potency of bLf, particularly by inhibiting the growth of tumour cells (Najmafshar et al. 2020).

In a different study, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay suggested that treatment with 500 μg/ml of isolated lactoferrin from bovine milk resulted in a very substantial reduction of the oesophageal cancer cell line (KYSE-30) by 53% and 80% after 20 and 62 hours, respectively, with no side effect on surrounding normal cells (Farziyan et al. 2015). Guedes and co-workers demonstrated that bLf selectively inhibits two highly metastatic cancers, namely prostate cancer and osteosarcoma cells during in vitro experiment (Guedes et al. 2018). In addition, bLf has shown inhibitory potential in chemically-induced colon cancer in rats by acting as a blocking and a suppressing agent, suggesting a promising feature of bLf as a chemopreventive agent for human colon carcinogenesis (Tsuda et al. 2006). BLf has been investigated in a comparative study with natural human lactoferrin (nhLf) on osteoblast. This study revealed that bLf possessed a more significant effect on osteoblast proliferation compared to nhLf in time- and dose-dependent manners (Zhang et al. 2018).

Although oral delivery provides the most favourable method for supplementing bLf, the bioavailability of orally administered bLf suffers from a number of factors associated with protein absorption (Yao et al. 2012). Studies suggested that bLf largely digested in the stomach due to enzymatic activity, resulted in protein degradation. Therefore, some approaches have been implemented to prevent bLf degradation and allow bLf to reach the small intestine, including microencapsulation, PEGylation, absorption enhancers, and iron saturation. Of these approaches, microencapsulation is the most used method to protect bLf from protease digestion (Superti 2020). Dix and Wright demonstrated that absorption of bLF appears to be enhanced with microencapsulation, as indicated by immune cell response (Dix and Wright 2018). Similarly, microencapsulation of Lf using bovine serum albumin and tannic acid showed enhanced release of Lf in small intestine than the control group with the same dose of free Lf (Kilic et al. 2017). Like lactoferrin, bovine immunoglobulins and other protein constituents also possess poor oral bioavailability. However, immunoglobulins were found less susceptible to enzymatic degradation than Lf. Some clinical studies suggest that orally administered immunoglobulins from BC could resist gastric exposure and complete proteolytic digestion in the gastrointestinal tract, and therefore can be used as natural remedies for patients with gastrointestinal disorders (Jasion and Burnett 2015).

## Future perspective: Bovine peptide-based radiopharmaceuticals

In recent years, the importance of naturally occurring peptides in the pharmaceutical arena is rising rapidly. Several peptides with various biological activities have been isolated from enzymatic hydrolysis of colostrum and milk-derived proteins in vitro and in vivo gastrointestinal digest. These peptides possess a wide range of health benefits such as antimicrobial, antithrombotic, opioid-like, immunomodulatory, and antihypertensive. It is worth noting that the majority of bioactive peptides are originated from caseins, whereas only a few peptides could be obtained from whey proteins (Birkemo et al. 2009; Jorgensen et al. 2010). Hence, casein is not only considered as an energy source but also as a substance that plays an important role in providing effective treatment of various ailments (Playford and Weiser 2021).

In nuclear medicine, the use of peptide-based radiopharmaceuticals (radiopeptides) has proved useful for diagnosis and therapy of many diseases, in particular cancers (Rangger and Haubner 2020). This approach was introduced into clinical settings more than two decades ago, allowing for cancer to be visualized and treated (Fani and Maecke 2012; Charron et al. 2016). Radiopharmaceuticals can be defined as unique medical formulation containing atoms of some radioactive elements that attached to drug molecules (Fichna and Janecka 2003). Since some receptors with small regulatory peptide ligands are overexpressed in cancers, radiopeptides could be used to target those receptors through a specific pathway. As a consequence, various radiopeptides are currently under investigation for both diagnostic imaging of cancer receptors and peptide receptor radionuclide therapy (PRRT) (Jamous et al. 2013). Therefore, like other natural peptides, bioactive peptides derived from BC also have the potential to be developed as new diagnostic or therapeutic agents.

To date, numerous bioactive peptides have been isolated from bovine milk, such as casocidin-1, casecidin 15 and 17, isracidin, caseicin A, B, and C. Casocidin-1 was isolated and identified by Zucht et al. as a cationic biopeptide from acidified bovine milk. This peptide showed potent antibacterial activity against *Staphylococcus carnosus* and *Escherichia coli* (Zucht et al. 1995). Casecidin 15, casecidin 17, and isracidin are antimicrobial peptides found naturally in fresh BC. These peptides have been reported to have potent antibacterial properties against *E. coli* (Birkemo et al. 2009). Caseicin A, B, and C are three peptides produced from the fragments of αs1-casein and exhibited antibacterial activity against two pathogenic strains of bacteria, namely *Enterobacter sakazakii* ATCC 12868 and *E. coli* DPC5063 (Hayes et al. 2006).

Some methods have been used to label peptides with radionuclides, including the direct introduction of radioactive atoms (direct radiolabelling) and indirect labelling using bifunctional chelating (BFC) agents (Edelmann et al. 2019). In general, radiolabelling peptides using radiometals requires the use of a BFC, while labelling using iodine radionuclide can be performed directly without the use of BFC (Dewulf et al. 2020). Several examples of BFC agents used for radiolabelling peptides include diethylene triamine pentaacetic acid (DTPA), 1,4,7-triazacyclononane-1,4,7-trisacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), and 1,4,8,11-tetraazacyclododecane-1,4,8,11-tetraacetic acid (TETA) (Fig. 1) (Jamous et al. 2013; Charron et al. 2016).

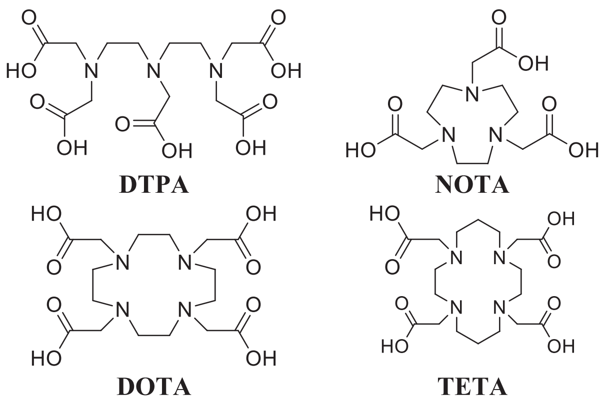


**Figure 1.** Chemical structure of several BFCs for peptide conjugation.

Furthermore, labelling of peptides can be performed via radioactive halogen isotopes, such as fluorine-18, bromine-76, iodine-131, and astatine-211 (Rangger and Haubner 2020). Direct radioiodination of peptides using potent oxidizing agents is one of the most extensively used

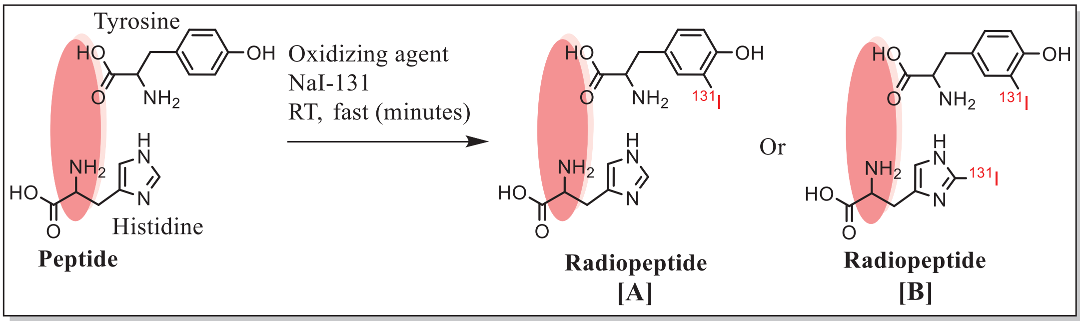


**Figure 2.** Schematic direct radioiodination of peptide with iodine-131. Radioiodination at physiological pH (~ 7.0) [A] and pH 8.0–8.5 [B].

strategy due to its simplicity and robustness, especially for peptides containing either tyrosine or histidine residue. The labelling site for iodination of peptides at physiological pH is tyrosine residues (Tolmachev et al. 2014; Mushtaq et al. 2018), but it may also involve the histidine residues if the pH is greater than 8.0–8.5 (Liddell 2002) (Fig. 2).

Some clinically relevant radionuclides that could be used for labelling naturally occurring peptides either for diagnosis or therapy purposes are summarized in Table 1 (Dash et al. 2013; Kawashima 2014; Wongso 2019; Zaheer et al. 2019; Rangger and Haubner 2020).

**Table 1.** Representative radionuclides used for peptide labelling and their physical parameters.

| Radionuclide | Half-life ($t_{1/2}$) | Type of Emission |
|---|---|---|
| Technetium-99m ($^{99m}Tc$) | 6.0 h | Υ |
| Gallium-68 ($^{68}Ga$) | 67.7 min | $\beta^+$, EC |
| Iodine-123 ($^{123}I$) | 13.2 h | EC, Υ |
| Iodine-124 ($^{124}I$) | 4.2 d | $\beta^+$, EC |
| Iodine-125 ($^{125}I$) | 59.4 d | EC, Υ |
| Iodine-131 ($^{131}I$) | 8.0 d | $\beta^-$, Υ |
| Scandium-44 ($^{44}Sc$) | 4.0 h | $\beta^+$ |
| Copper-64 ($^{64}Cu$) | 12.7 h | $\beta^+$, EC, $\beta^-$ |
| Bromine-76 | 16.2 h | $\beta^+$, EC |
| Fluorine-18 ($^{18}F$) | 109.8 min | $\beta^+$, EC |
| Carbon-11 ($^{11}C$) | 20.4 min | $\beta^+$, EC |
| Astatine-211 | 7.2 h | α, EC |
| Zirconium-89 | 78.4 h | $\beta^+$, EC |
| Yttrium-90 | 64.1 h | $\beta^-$ |
| Lutetium-177 | 159.4 h | $\beta^-$ |

Υ: gamma ray emission; $\beta^+$: positron emission; $\beta^-$: electron emission; EC: electron capture.

## Conclusion

BC is considered a rich source of bioactive constituents that possesses several pharmacological activities such as anti-infective, anti-inflammatory, and anticancer. Until recently, BC has been used as a nutraceutical (a compound that is used for both food and medical remedies). Although bioactive peptides have been recognized as a privileged precursor for peptide-based radiopharmaceuticals eligible for detection and treatment of various diseases, the use of peptides from BC remains largely unexplored. Therefore, in-depth studies and novel strategies should be implemented to explore the role of bovine peptides and to achieve BC-based peptides application in clinical settings, especially in nuclear medicine.

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