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Peptide-Based Radiopharmaceuticals: Pharmacological Properties and Potential Applications of Bovine Colostrum – A Review

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ABSTRACT

Bovine colostrum (BC), the first milk produced by cows postpartum, has been traditionally utilized in managing various human conditions, including infections, inflammatory disorders, and cancers. Emerging research highlights bovine lactoferrin and bovine antibodies as the primary bioactive components responsible for BC's therapeutic effects. Consequently, BC has also been examined for its potential to offer short-term protection against COVID-19. Moreover, it holds promise as a source for peptide-based radiopharmaceutical development. To date, multiple bioactive peptides have been identified in BC, such as casocidin-1, casecidin-15 and -17, isracidin, and caseicins A, B, and C. Similar to other bioactive peptides, these BC-derived peptides may serve as valuable precursors for radiopharmaceuticals intended for diagnostic or therapeutic applications. This review summarizes the pharmacological activities of bovine colostrum and explores the potential of its peptides in the design of radiopharmaceuticals for nuclear medicine.

Keywords: Antibodies, Bovine colostrum, Biological activities, Radiopharmaceuticals, Peptides

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Introduction

Bovine colostrum (BC) is the nutrient-rich secretion produced by cows during the first days following parturition, offering significant potential to enhance health by supporting immune function. In dairy cattle, antibodies are actively transported from mammary epithelial cells into the mammary gland through receptor-mediated processes, resulting in high concentrations of these immunoglobulins in colostrum [1, 2]. BC is abundant in nutrients and bioactive molecules, including carbohydrates, proteins, lipids, immunoglobulins, vitamins, minerals, antimicrobial proteins such as lactoferrin, lysozyme, and lactoperoxidase, as well as growth factors [3, 4]. Notably, the levels of many bioactive components decline sharply within three days postpartum, highlighting the critical importance of colostrum produced immediately after calving. Consequently, BC not only provides essential nutrition but also confers passive immunity, enhances immune system maturation, supports growth, facilitates tissue repair, and promotes overall development in newborns [5-7].

Beyond its role in calf health, BC is recognized as a valuable dietary supplement for humans due to its rich biological and nutritional properties [8]. Its bioactivity may vary between species or be species-specific, indicating potential benefits for particular human populations [9]. The composition of BC is influenced by multiple factors, such as breed, health status, parity, nutrition, length of the dry period, and the time elapsed after calving [3, 10]. Therefore, the immunological effects of a specific BC product cannot be generalized to all colostrum sources. Immunoglobulin G (IgG) is the predominant antibody in BC, followed by immunoglobulin A (IgA) and immunoglobulin M (IgM), which play essential roles in defending against microbial pathogens and neutralizing toxins [11].

The impact of BC immunoglobulins on human health, particularly immune function, has been extensively investigated and remains an active area of research. Emerging evidence suggests that BC-derived IgG can bind to

a wide array of bacteria, viruses, and allergens [11]. In vitro studies have demonstrated that polyvalent BC immunoglobulins, combined with vitamin D3, can modulate cytokine production and systemic inflammation in colorectal cancer patients by reducing pro-inflammatory markers and enhancing anti-inflammatory cytokines, indicating potential as a novel therapeutic approach in cancer and immune-related conditions [12]. Additionally, BC has shown promise against respiratory infections, including SARS, avian influenza, and other human respiratory pathogens [2]. More recently, bioactive compounds from both vaccinated and unvaccinated cows have been reviewed for their potential to provide temporary protection against SARS-CoV-2 infection (COVID-19), offering an interim therapeutic option until vaccines are widely accessible [13, 14].

Historically, BC has been used to treat infections and other health issues associated with immune deficiency before the advent of antibiotics [15]. Current research continues to highlight its role in regulating physiological and protective mechanisms in conditions such as inflammation and cancer. For example, orally administered bovine lactoferrin (bLf) has demonstrated pharmacological effects in preventing infection, mitigating inflammation, and reducing carcinogenic processes [16]. This review aims to summarize the most significant health-promoting activities of BC, including its anti-inflammatory, anticancer, and anti-infective properties, and to explore its potential application in the development of peptide-based radiopharmaceuticals. A systematic literature search was conducted across Scopus, ScienceDirect, Medline, PubMed, and Google Scholar using keywords such as bovine colostrum, cow's milk, immunoglobulins, antibodies, antiviral, antibacterial, anti-inflammatory, anticancer, radiolabelling, radionuclides, peptides, and radiopharmaceuticals.

Anti-infective activities of BC

A wide range of antimicrobial agents has been identified for combating infectious diseases [17]. Evidence indicates that bioactive components in bovine colostrum (BC) may exert effects beyond local action, contributing to immune networks and triggering systemic responses after interaction with the gut mucosa [9]. In vitro studies have shown that bovine immunoglobulins can interact with pathogens to prevent infections, reduce gastrointestinal inflammation, inhibit bacterial proliferation, and strengthen the intestinal barrier [11]. Among BC components, bovine lactoferrin (bLf) has emerged as a key molecule demonstrating both bacteriostatic and bactericidal effects in preclinical and clinical contexts. Its anti-infective properties are primarily mediated through two mechanisms: sequestration of free iron at infection sites, limiting microbial access to this essential nutrient, and direct disruption of microbial cell membranes [18].

Anand and colleagues reported that bLf can interact with host cells, such as red blood cells and macrophages, in a manner influenced by the iron saturation status of lactoferrin. Incubation with iron-saturated bLf enhanced phagocytic activity, reactive oxygen species production, and Toll-like receptor expression [19]. Clinically, Hu *et al*. demonstrated that oral immunotherapy using bovine antibodies significantly controlled Helicobacter pylori infection; 13 of 30 treated patients tested negative after 28 days of therapy based on the C-14 urea breath test [20]. Additionally, concentrated late-stage skimmed BC, which is rich in IgG, exhibited inhibitory effects against human rotavirus (HRV) in vitro, suggesting potential use as a natural therapeutic, particularly for immunocompromised populations such as children and the elderly [21]. Bojsen *et al.* reported that adding bovine macromolecular whey protein (MMWP) could reduce infection by multiple rotavirus strains—including human (Wa), bovine (RF), porcine (YM), and simian (RRV)—in human intestinal cell lines (FHs 74 Int and Caco-2) [22]. Gunaydin and colleagues further demonstrated that combining hyperimmune BC (HBC) with an engineered probiotic (Lactobacillus rhamnosus GG) reduced diarrhea duration in rotavirus-infected mice more effectively than HBC alone [23].

Anti-inflammatory activities of BC

Bovine lactoferrin has also been widely recognized for its anti-inflammatory effects in both preclinical and clinical studies [18]. BC's anti-inflammatory activity is largely linked to its ability to modulate cytokines, including interleukins (IL-1β, IL-2, IL-6, IL-17), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and other non-antimicrobial bioactive molecules. Studies suggest that BC may help maintain gut homeostasis and mitigate inflammation in gastrointestinal disorders [9]. For example, treatment of Caco-2 and HT29 cells with BC reduced IL-8 levels following TNF-α exposure [24]. BC also modulates Toll-like receptor 4 (TLR4), gut microbiota, and pro-inflammatory cytokines in animal models of colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) [7].

When combined with glutamine, BC has demonstrated enhanced efficacy in preventing NSAID-induced intestinal damage and bacterial translocation in animal models, outperforming either treatment alone [25]. Other studies have shown that BC reduces natural killer (NK) cell and monocyte activity, modulates lymphoproliferative responses to lipopolysaccharide (LPS), stimulates IFN-γ, IL-10, and IL-2 production in human peripheral blood mononuclear cells, and inhibits intestinal epithelial inflammation through suppression of the NF-κB pathway [5, 15, 26]. In mouse models of collagen-induced arthritis, BC administration reduced disease symptoms [27].

Oral administration of bLf appears to act as an effective systemic immune modulator by first influencing intestinal immunity and subsequently enhancing systemic immune responses. Studies indicate that bLf promotes IL-8 production in intestinal epithelial cells, increases CD4+, CD8+, and NK cell populations in the gut mucosa, and boosts immune cell numbers in lymph nodes and spleen, while supporting Th1-type cytokine synthesis (IP-12 and IFN-γ), which may be critical for controlling inflammation [28].

Anticancer activities of BC

Cancer remains a major global health challenge, with substantial unmet medical needs [29, 30]. Conventional treatment modalities, including chemotherapy, surgery, radiotherapy, bone marrow transplantation, or combinations of these approaches, often face limitations and adverse effects. For instance, chemotherapy can lead to toxicity in vital organs and drug resistance, radiotherapy may cause collateral damage to surrounding healthy tissue, and surgical intervention sometimes fails to remove all malignant cells, increasing the risk of tumor recurrence [31, 32]. Consequently, there is an urgent demand for safe, cost-effective therapies that minimize side effects while improving patient outcomes [33]. The exploration of bovine milk proteins as natural anticancer agents has emerged as a promising avenue, supported by encouraging preliminary findings [31].

Bovine colostrum (BC) contains two major protein classes: caseins and whey proteins. Among the bioactive molecules, lactoferrin—a globular glycoprotein of approximately 80 kDa within the casein fraction—has been extensively studied for its antioxidant, anti-inflammatory, and anticancer properties [34]. Mounting evidence from preclinical and clinical studies demonstrates that bovine lactoferrin (bLf) exhibits diverse anticancer effects, likely mediated through multiple cellular mechanisms, including enhancement of immune function, regulation of carcinogenic enzymes, inhibition of angiogenesis, and induction of apoptosis [18]. Zhang *et al*. reported that bLf significantly inhibited the proliferation of various breast cancer cell lines (MCF-7, T-47D, Hs578T, and MDA-MB-231) within 48 hours of treatment [35]. Similarly, Najmafshar and colleagues demonstrated that immobilizing bLf on graphene oxide augmented its anticancer activity, particularly by suppressing tumor cell growth [36].

In another study, the MTT assay revealed that treatment of the oesophageal cancer cell line (KYSE-30) with 500 µg/ml of isolated bovine lactoferrin reduced cell viability by 53% and 80% after 20 and 62 hours, respectively, without affecting surrounding normal cells [37]. Guedes *et al*. further demonstrated that bLf selectively inhibited highly metastatic prostate cancer and osteosarcoma cells in vitro [38]. Moreover, in chemically induced colon cancer models in rats, bLf functioned both as a blocking and suppressive agent, indicating potential chemopreventive effects against human colorectal carcinogenesis [39]. Comparative studies with natural human lactoferrin (nhLf) also suggest that bLf more effectively stimulates osteoblast proliferation in a time- and dose-dependent manner [40].

Although oral administration represents the most convenient route for bLf supplementation, its bioavailability is limited by protein degradation during absorption [41]. Gastric enzymatic activity can significantly degrade orally delivered bLf, reducing its efficacy. To overcome these challenges, strategies such as microencapsulation, PEGylation, use of absorption enhancers, and iron saturation have been employed, with microencapsulation being the most widely applied to protect bLf from proteolysis [18]. Dix and Wright reported that microencapsulated bLf showed improved absorption, as evidenced by enhanced immune responses [42]. Similarly, microencapsulation using bovine serum albumin and tannic acid enhanced lactoferrin release in the small intestine compared to free bLf at equivalent doses [43].

Like lactoferrin, other BC proteins, including immunoglobulins, exhibit poor oral bioavailability. However, immunoglobulins are less susceptible to enzymatic digestion than bLf. Clinical studies indicate that orally administered bovine immunoglobulins can resist gastric degradation and maintain their functional integrity throughout the gastrointestinal tract, supporting their use as natural therapeutic agents for gastrointestinal disorders [44].

Future perspective: bovine peptide-based radiopharmaceuticals

The therapeutic potential of naturally occurring peptides has gained significant attention in recent years due to their versatile biological activities. Enzymatic digestion of colostrum and milk proteins, both in vitro and within the gastrointestinal tract, has yielded numerous bioactive peptides. These molecules exhibit a wide array of health-promoting effects, including antimicrobial, antithrombotic, opioid-like, immunomodulatory, and blood pressure-lowering actions. Interestingly, most of these peptides are derived from casein proteins, while whey proteins contribute only a small fraction of bioactive sequences [45, 46]. Consequently, caseins are not merely energy sources but also serve as precursors for compounds with potential therapeutic applications [47].

In the field of nuclear medicine, peptide-based radiopharmaceuticals, commonly called radiopeptides, have emerged as valuable tools for both diagnostic imaging and targeted therapy, particularly in oncology [48]. Introduced into clinical practice more than twenty years ago, these agents allow tumors to be detected and treated via specific molecular interactions [49, 50]. Radiopharmaceuticals are specialized compounds in which radioactive isotopes are chemically linked to pharmacologically active molecules [51]. Since many cancers overexpress receptors for small regulatory peptides, radiopeptides can exploit this property to deliver radiation selectively to malignant cells. As a result, both diagnostic imaging and peptide receptor radionuclide therapy (PRRT) are active areas of investigation [52]. By extension, peptides originating from BC could similarly be explored as new molecular tools for imaging or therapeutic purposes.

Several bioactive peptides have already been characterized from bovine milk. For instance, casocidin-1, a positively charged peptide isolated from acidified milk by Zucht *et al*. exhibits strong antibacterial activity against Staphylococcus carnosus and Escherichia coli [53]. Casecidin 15, casecidin 17, and isracidin, naturally present in fresh BC, have demonstrated similar antibacterial properties against E. coli [45]. Additionally, peptides derived from αs1-casein, including caseicin A, B, and C, have shown potent activity against Enterobacter sakazakii ATCC 12868 and E. coli DPC5063 [54].

Techniques for coupling peptides with radionuclides include direct incorporation of radioactive atoms and indirect labelling using bifunctional chelating (BFC) agents [55]. Radiometal labelling generally requires a BFC, whereas iodine radionuclides can often be attached directly without chelators [56]. Common BFC molecules 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) **(Figure 1)** [50, 52].

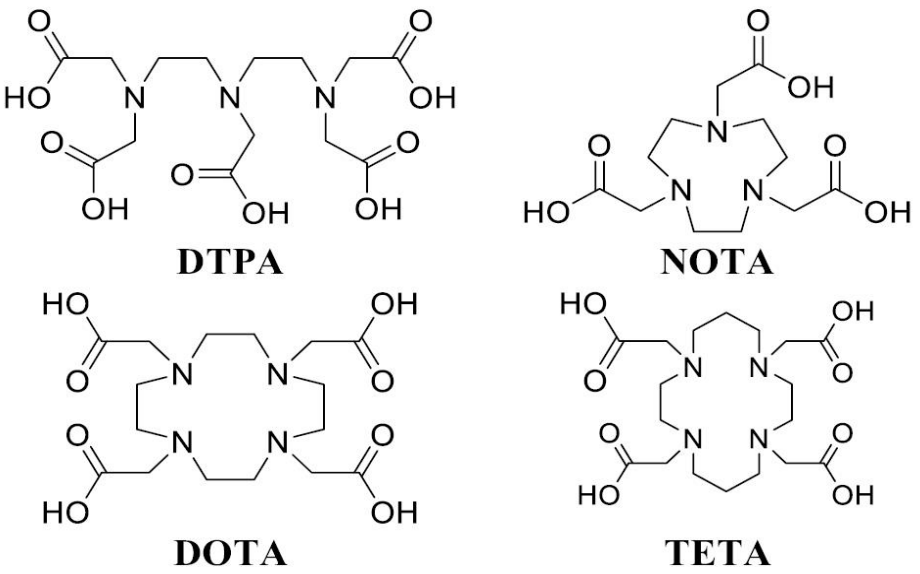

Figure 1. Chemical structures of selected BFCs for peptide attachment.

Peptides can also be tagged using radioactive halogen isotopes such as fluorine-18, bromine-76, iodine-131, and astatine-211 [48]. Among these methods, the direct radioiodination technique—employing strong oxidizing agents—is widely favored because of its straightforwardness and reliability. This approach is especially suitable for peptides that contain tyrosine or histidine residues. At physiological pH, iodination predominantly occurs at

tyrosine sites [57, 58], whereas at higher pH values above 8.0–8.5, histidine residues can also be modified [59] **(Figure 2)**.

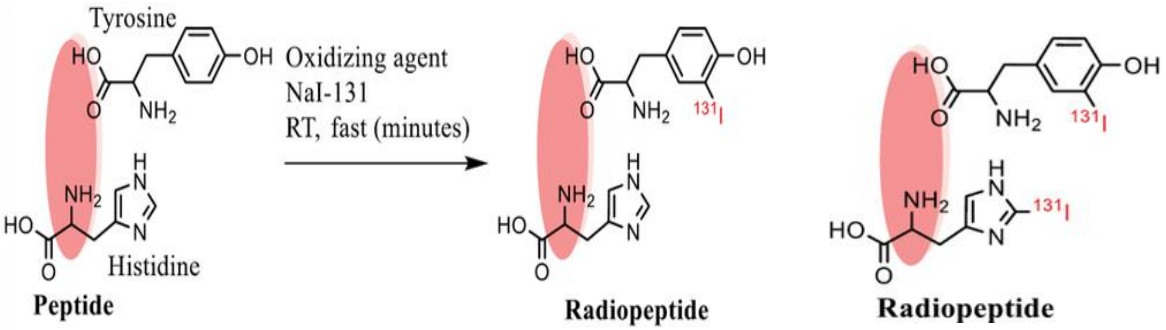

Figure 2. Illustration of direct peptide radioiodination using iodine-131. Radioiodination at physiological pH (~7.0) [a] and at elevated pH 8.0–8.5 [b].

Table 1 provides an overview of clinically relevant radionuclides that can be employed for labelling naturally occurring peptides for either diagnostic or therapeutic applications [48, 60-63].

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	Y
Gallium-68 (^{68}Ga)	67.7 min	β^+, EC
Iodine-123 (^{123}I)	13.2 h	EC, Y
Iodine-124 (^{124}I)	4.2 d	β^+, EC
Iodine-125 (^{125}I)	59.4 d	EC, Y
Iodine-131 (^{131}I)	8.0 d	β-, Y
Scandium-44 (^{44}Sc)	4.0 h	β^+
Copper-64 (^{64}Cu)	12.7 h	β^+, EC, β-
Bromine-76	16.2 h	β^+, EC
Fluorine-18 (^{18}F)	109.8 min	β^+, EC
Carbon-11 (^{11}C)	20.4 min	β^+, EC
Astatine-211	7.2 h	α, EC
Zirconium-89	78.4 h	β^+, EC
Yttrium-90	64.1 h	β-
Lutetium-177	159.4 h	β-

Y: gamma ray emission; β^+: positron emission; β-: electron emission; EC: electron capture.

Conclusion

Bovine colostrum (BC) is a valuable reservoir of bioactive compounds exhibiting multiple pharmacological effects, including antimicrobial, anti-inflammatory, and anticancer activities. Traditionally, BC has been utilized as a nutraceutical, serving both dietary and therapeutic purposes. While bioactive peptides are increasingly recognized as promising candidates for developing peptide-based radiopharmaceuticals for disease diagnosis and therapy, peptides derived specifically from BC have not yet been fully explored. Consequently, further comprehensive research and innovative approaches are needed to investigate bovine peptides and to advance their potential applications in clinical practice, particularly within the field of nuclear medicine.

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