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REVIEW

Bioactive Peptides from Bovine Colostrum: Sources, Structures, and Biomedical Applications

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Abstract
Bovine colostrum (BC) is the first milk produced in the first few days after birth, notable for its high concentration of nutrients and immune factors, and clearly distinct from mature milk. Colostrum contains numerous proteins and bioactive peptides derived from them that support the growth, development, and immunological defenses of newborns. These peptides are primarily derived from major colostral proteins such as caseins, immunoglobulins (Igs), lactoferrin (Lf), and α-lactalbumin (α-La) through the action of digestive and enzymatic processes. These peptides possess antimicrobial, antitumor, anti-inflammatory, antifungal, antihypertensive, antioxidant, antiviral, and antiparasitic properties and are worthy of significant research. Recent studies have highlighted their role in enhancing mucosal immunity, maintaining gut integrity, promoting tissue regeneration, and preventing microbial infections. However, challenges such as low bioavailability, enzymatic degradation, and regulatory limitations restrict their clinical translation. Advances in delivery systems-such as encapsulation and nanoformulations-have shown promise in improving their stability and targeted action. Based on these studies, BC-derived bioactive peptides appear to have promising potential in many diseases and clinical applications in the future. This review shows a comprehensive summary of the sources, molecular characteristics, and biomedical applications of BC-derived peptides, emphasizing their potential as multifunctional agents in health promotion and disease prevention.

Keywords Bovine colostrum · Bioactive peptides · Functional foods · Mucosal immunity · Proteomics

Introduction

Bovine colostrum (BC) is a liquid secreted by mammals in the early postnatal period (2 to 5 days postpartum) after birth, contains dense nutrition and immunity elements and is obviously different from mature milk. This liquid, named as pre-milk or colostrum, is crucial for the newborn calf to survive and grow healthy [1]. BC is particularly remarkable for its high concentration of especially IgG, Lactoferrin (Lf), lysozyme, oligosaccharides (OS) and growth factors (e.g. epidermal growth factor (EGF)) [2, 3].

Biochemical content of BC is notable for its structure very similar to plasma and in this respect, it has much more concentrated structure compared to normal milk. Unlike mature milk, colostrum contains higher amounts of protein, lipid, mineral and fatty acid; the lactose ratio is usually lower [4]. For its content that contains bioactive peptides and protein derivatives, functional nutrition compounds, it provides promising findings that it may have various therapeutic effects [2–4]. Therefore, BC is considered as a natural biological source that can be used both directly for immune and growth functions and in clinical and nutritional applications.

Among newborns lacking fully developed immune responses, BC compounds provide passive immunity. Additionally, colostrum significantly contributes to strengthening the gut barrier, balancing the intestinal microbiota, and protecting against pathogens. In humans, as in newborn calves, colostrum not only provides immune system support

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but also serves as a valuable nutritional supplement due to its high content of bioavailable proteins, vitamins (A, D, E, K), and minerals [5, 6]. Growth factors and antimicrobial peptides found in colostrum have a positive impact on musculoskeletal system repair and tissue growth [5]. Multidisciplinary research in the literature indicates that colostrum provides several health benefits, including immune regulation, support of gastrointestinal health, and the promotion of growth and development. It has also been reported that BC may help prevent or alleviate the symptoms of certain viral and bacterial infections [6].

Milk and colostrum are crucial resources of proteins with certain multifunctional features. Additionally, BC's structure includes bioactive peptides encoded in the structure of the original protein, which play vital roles in supporting the immune system and facilitating various physiological processes [7, 8]. The characteristic of bioactive peptides diversifies by the length and sequence of amino acids. These peptides are generated through the digestion of their parent proteins. Various peptide derivatives including inhibitory activity against angiotensin-converting enzyme (ACE) were stated as a result of colostrum degradation by proteolytic enzymes, including pepsin, trypsin, and chymotrypsin [9]. When compared with mature milk, BC shows enhanced levels of total protein, largely due to elevated concentrations of Igs and casein [7]. On the first day after birth, the protein content in colostrum can reach approximately 15%, whereas it declines to around 3% in mature milk. Colostrum proteins are generally categorized into soluble whey proteins (such as α-Lactalbumin (α-La)), β-lactoglobulin, and Lf and insoluble proteins like caseins, both of which possess not only nutritional but also significant biological functions. Casein, which constitutes about 75% of total cow's milk proteins—with αs1-casein being the predominant form—is broken down during digestion into opioid-like peptides that can modulate immune responses and delay gastric emptying. Moreover, casein plays a protective role by reducing the digestion rate of other bioactive proteins, such as insulin-like growth factor 1 (IGF-1) and EGF, through competitive inhibition, thereby enhancing their bioavailability [7].

Colostrum, rich in bioactive proteins and peptides, stands out as a powerful natural substance with both nutritional and therapeutic benefits. Studies have shown that it can prevent exercise-induced immune suppression, support gastrointestinal integrity, and aid in the treatment of conditions such as ulcerative colitis and infectious diarrhea, highlighting its clinical relevance [10]. With advances in milk processing technologies, colostrum-derived components are now incorporated into functional foods like yogurt and supplements, offering additional health benefits such as immune support, antioxidant activity, and improved gut balance [5, 11]. Clinically, colostrum has been effective in improving outcomes in diseases like Crohn's, chemotherapy-induced mucositis, and necrotizing enterocolitis (NEC), by promoting epithelial regeneration, reducing intestinal permeability, and preventing microbial translocation [12–14]. Its components, such as Lf and α-La derivatives, exhibit antimicrobial, immunomodulatory, and even anticancer properties by inducing apoptosis and inhibiting tumor spread [14]. Thanks to its low toxicity and natural biocompatibility, colostrum is also being investigated for use in drug delivery systems, biomaterial coatings, and neonatal health products, reinforcing its potential as a multifunctional agent in biomedical applications [5, 14]. Although recent studies have begun to explore colostrum from other animal species, this review focuses specifically on BC in terms of its nutritional value, biologically active peptides, and its biomedical application potential for human health. Trypsin, a serine protease of pancreatic origin, has a wide range of applications from food technology to proteome analysis, from the regulation of soy protein allergenicity to the production of antihypertensive peptides and as a biomarker for various diseases (e.g. pancreatitis, cystic fibrosis) [15]. Therefore, it is important to develop simple, sensitive and selective biosensors for the evaluation of trypsin activity. BC contains glycoprotein trypsin inhibitors that protect the immune and growth factors contained in colostrum from proteolytic degradation under digestive conditions in the human stomach [16, 17]. It has been stated that the therapeutic effect of colostrum cannot be sustainable in the absence of these inhibitors [18]. In particular, bovine trypsin inhibitor supports the maintenance of functional stability in bioactive elements like Igs and growth factors by slowing down trypsin-mediated digestion in the gastrointestinal environment [16, 17]. These inhibitors also support the protection of proteins with biological activity against proteolytic degradation in the intestine [18]. Pepsin is a gastric aspartic endoprotease with highly pH-dependent activity and is responsible for the hydrolysis of approximately 20–30% of proteins in the gastric phase of digestion [16, 19]. This enzyme is a nonspecific protease, usually monomeric, with broad substrate specificity; it hydrolyzes peptide bonds, especially those containing hydrophobic and aromatic amino acid residues (e.g. tryptophan, tyrosine, and phenylalanine), but shows low activity against bonds containing valine, alanine or glycine [20]. Pepsin can also be obtained from different sources, e.g. gastric tissues of seafood and fish, and depending on these sources, its biochemical properties such as molecular weight (Mw), optimum pH and temperature may vary [21]. However, the high proteolytic capacity of pepsin threatens the structural integrity of sensitive molecules, especially in biological fluids rich in IgG, IgA; EGF, IGF-I/II, Transforming growth factor-β(TGF-β) and antimicrobial proteins (Lf, lysozyme) such as BC [16]. Indeed, in one study, the proliferative activity of

BC decreased 61% after HCl/pepsin and chymotrypsin (CT) exposure; however, this loss decreased to 50% when colostrum coadministered with soy and was significantly reduced against the loss of bioactive components such as IgG, EGF, TGF-β and Lf. Proteases (proteinases or peptidases) are a class of hydrolase enzymes that cleave peptide chains in proteins [22]. These enzymes hydrolyze peptide bonds in peptides and proteins to produce smaller peptides or free amino acids and are widespread in all living organisms; in fact, they make up about 2% of the human genome [23]. Proteases are divided into two main groups when classified according to the position of the bond they act on: endopeptidases hydrolyze peptide bonds in the internal regions of proteins to form shorter peptide chains; exopeptidases hydrolyze bonds in the C-terminal or N-terminal region of the substrate to release free amino acids [22]. Major sources of these enzymes include animal tissues (e.g. beef stomach), plants (e.g. pineapple, figs, papaya) and microorganisms (e.g. *Bacillus spp.*, *Pseudomonas spp.*) [22]. Microbial proteases in particular are more widely preferred in industrial applications than animal and plant-derived proteases due to their higher stability, ease and speed of production, small footprint, cost-effectiveness, high yield and consistency, and suitability for process optimization and genetic modification [24]. Microbial proteases can be divided into several subcategories according to their structural and functional properties: (1) those that can hydrolyze by targeting specific proteins (e.g. collagenase, elastase, keratinase); (2) those with similarities to classical proteolytic enzymes (e.g. chymotrypsin, trypsin, pepsin); (3) those active in different pH ranges (acidic, alkaline or neutral); (4) those classified according to their catalytic mechanism (e.g. aspartic, cysteine, serine proteases and metalloproteases carrying specific amino acid residues in their active sites); (5) those acting as endopeptidases or exopeptidases according to their action on the substrate [22]. Thanks to their diversity, microbial proteases are widely utilized in therapeutic applications not only in food and biotechnology but also in various medical fields such as lung, heart, digestive, eye diseases, skin ulcers and pain management [22, 24].

Despite the increasing literature on BC and its functions, the comprehensive synthesis that focuses on bioactive peptides derived from major proteins is still limited. Individual studies have been characterized antimicrobial, immunomodulatory and regenerative effects of specific peptide fractions, but the structural determinants underlying these biological activities and their translational importance have not been systematically integrated. Thus, this review aims to represent a general vision that is detailed and structured including sources of bioactive peptides derived from major proteins of BC, their molecular structures and effects mechanisms. Also we emphasized their emerging biomedical applications and therapeutic potentials by examining their antimicrobial, anti-inflammatory, immune regulatory and tissue regenerative effects critically. This review aims to enhance the existing understanding in the antimicrobial and bioactive proteins field and provide an accurate environment for upcoming research and clinical translation.

Proteins as a Source of Bioactive Peptides

BC exhibits a specific protein profile that is rich in bioactive compounds such as Lf, immunoglobulins (Igs) and growth factors compared to mature milk [1]. This structural difference constitutes a fundamental source for production of unique bioactive peptides in the result of proteolytic processes. Especially, the high amount of Lf content promotes the production of antimicrobial and immunomodulatory peptides such as lactoferricin and lactoferrampin. As a result, peptide profiles of colostrum and mature milk can not be regarded as equal to each other in the perspective of substrate diversity and functional outcomes. Bioactive peptides are determined as encrypted sequences masked in the main protein structure. These sequences become functional being released by biochemical processes such as digestion, enzymatic hydrolysis and fermentation. Biological potential of a peptide does not arise from only the quantity of main protein as much as disposition to proteolysis due to their cationic, amphipathic or prolin-rich structural motives. Especially colostrum in the early lactation, constitutes base to these defense mechanisms by representing a different "precursor pool" from standard milk composition. However, although the success of these mentioned peptides in laboratory conditions, limitation of in vivo and bioavailability data, that show its effects on real organisms, continues to be the most remarkable deficiency.

Lactoferrin

Lf at high concentrations in BC is a versatile glycoprotein that is structurally included in the transferrin superfamily. This protein, thanks to its high affinity iron-binding capacity, lies at the heart of the colostrum's immunomodulatory and antioxidant potential [25–27]. Lf concentration in BC, represents a more dominant profile compared to mature milk by remaining at approximately 0.80–0.83 mg/mL. This high concentrated presence allows the Lf to play a role as a fundamental bioactive compound for fulfilling early stage passive immunity of newborn [3, 5]. Lf, which has a diverse biological activity spectrum, takes on a versatile barrier function in the host defense system thanks to their anti-inflammatory, antioxidant and immunomodulatory effects. This glycoprotein, besides protecting mucosal integrity by

blocking adhesion of pathogens at the molecular level, especially optimizes gut maturation and barrier functions in the premature neonatal stage [3, 28–30]. Functional stability and biological activity of Lf, take shape by modulation of *N*-glycan structures that bind to protein skeleton. These glycan compounds directly contribute to pleiotropic effects on host organisms by determining Lf's antigenic and immunogenic profile besides optimizing structural parameters such as; protein folding, solubility and resistance against proteolysis [29]. It also contributes to bone formation by promoting osteoblast proliferation and the release of growth factors [5]. The presence of Lf receptors in various immune cells such as intestinal tissue, neutrophils, monocytes, macrophages, lymphocytes and platelets shows that it plays an active role in the modulation of immune responses [5]. In addition, it has wide applications in both medical and food technology due to its effects in preventing lipid oxidation and supporting microbial flora balance. Bovine-derived Lf, which is accepted as "generally recognized as safe" (GRAS) by the Food and Drug Administration (FDA), is used in cosmetic and nutraceutical formulations as well as dietary products like baby food, yogurt, beverages and bakery products [29]..

Caseins (α-, β-, κ-)

Caseins have a heterogeneous micelle structure that can be separated from whey proteins in pH 4.6 which is their isoelectric level. This fractional separation has a critical importance in terms of including precursor bioactive peptide sequences that occur during digestion process and have specific regulatory effects on biological systems [31]. Structurally, it is generally considered an essentially unstructured protein, devoid of secondary structure. The casein complex in BC represents a heterogeneous system composed from four main phosphoprotein fractions consisting of αs1-, αs2-, β- and κ-casein. Predominantly, α- (%52,7) and β- (%36,8) caseins play a dominant role in this fractional distribution. Every subunit constitutes a rich precursor source for synthesis of unique bioactive peptide sequences with different effects during proteolytic digestion [31]. The protein matrice in BC exhibits a unique distribution between casein and whey fractions in the range of 92/8 ratio. This specific protein ratio is not only a structural feature it also optimizes regulatory role of colostrum on neonatal immunity system by forming a kinetic base that is determining factor for the release of casein-derived bioactive peptides and the bioavailability of essential nutrient components (Table 1) [31, 32].

Table 1 Types of casein and their functions

Casein Subtype	Functions	References
αs1-casein	Strongly binds calcium phosphate, contributing to micelle formation.	[33–35]
αs2-casein	Has high phosphate content and enhances micelle stability through calcium binding. Enhances calcium absorption and bone health.	[33–36]
β-casein	Improves solubility and digestibility. Easier to digest; may reduce allergic responses.	[33–35, 37]
κ-casein	Prevents micelle aggregation. Stabilizes milk proteins; beneficial for gut health during digestion.	[33–35, 37]

Immunoglobulins (IgG, IgA)

BC, composed of IgG1, IgM, IgA and IgG2 isotypes, has a dense Ig matrice that structures the basis of neonatal passive immunity. This various antibody profile determines the biological value of colostrum by forming a broad-spectrum humoral defense shield against luminal and systemic pathogens [38–40]. These are subcategorized based on their mechanism of existence, for example, IgG and IgA as monomers, dimeric IgA, or pentameric IgM — which initiate antimicrobial responses. The underlying mechanisms of action of Ig include preventing surface adhesion of microbes, inhibiting bacterial metabolism, agglutination of bacteria, and neutralizing toxins and viruses [38]. These mechanisms are carried out with high efficiency by IgM antibodies. IgG, found in the greatest concentrations, exhibit diverse modes of action [39]. It can promote bacterial destruction via complement activation or stimulate phagocytic clearance through opsonization [38]. Igs are complex glycoprotein structured effector molecules which show function thanks to their capacity of antigen-specific recognition and neutralization in the host defense system. These humoral compounds play a role as a bridge in preventing infections and triggering immune cascade by binding pathogenic epitopes with high affinity. Upon encountering a foreign antigen, B cells—through their antigen-specific receptors—differentiate into plasma cells that secrete antibodies sharing the same specificity [39]. These antibodies exhibit high specificity and affinity for their target antigens, mediating several immune responses such as complement activation, enhanced phagocytosis via opsonization, and mast cell activation [38]. IgG subclasses represent a division of labor specialized for their antigenic targets. In this hierarchy, IgG1 and IgG3 fundamentally defuse protein structured antigens. On the other hand IgG2 focuses on polysaccharide-encapsulated pathogens, meanwhile IgG4 act as an anti-inflammatory regulator in chronic antigen exposition [39]. The most fundamental feature that characterizes the immunological profile of BC is the IgG1 isotype, which accounts for approximately 80–90% of the total Ig content. IgM and IgA, which are other critical compounds of neonatal defense, complete the capacity of humoral immunity of colostrum by accompanying this

dominant fraction [41]. In the first hours after birth, IgG concentration in colostrum reaches high values such as 50–100 mg/mL; this is due to the fact that passive immunity is provided only through colostrum due to the absence of placental transmission in cows [5]. IgGs have versatile immunological functions such as neutralization of pathogens, shaping of intestinal microbiota, stimulation of local IgA production and activation of B/T cell responses [1, 5, 7]. Colostrum quality is largely dependent on IgG concentration, and levels of ≥50 mg/mL are generally considered "good colostrum". With both specific and nonspecific immune effects, Igs demonstrate the importance of colostrum as both a protective and supportive biological agent [5, 41].

α-Lactalbumin

α-La, which is naturally found in human and ruminant milk, is a functional glycoprotein that provides its structural stability via calcium ions. This protein directly modulates the catalytic activity of synthase enzymes. Also it is an essential biochemical compound in regulation of lactose levels in milk composition and secretional activity of breast tissue [42]. α-La, which is found at an average of 2.44 ± 0.64 g/L in human milk, constitutes 22% of total protein and 36% of whey proteins; while these rates are 3.5% and 17% in bovine milk, respectively. This quantitative gap is a critical parameter that determines the fundamental difference between essential amino acid profile of human milk and their digestibility capacity [3]. In BC, as shown in Fig. 1., α-La is found in significant amounts despite the high density of Igs, Lf, and growth factors, and plays an involvement in critical biological processes such as intestinal development, mineral absorption, antioxidant defense, and immune system support in newborn calves [3]. α-La, which has a high nutritional value, is widely used in baby foods and dietary supplements, particularly because of its structural and compositional resemblance to human milk. Owing to its emulsifying and solubilizing capabilities, it contributes significantly to the development of stable emulsions and formulations in the food industry [42]. In addition, in recent years, α-La has attracted attention as a promising biomaterial in nanotechnology applications to achieve encapsulation and targeted delivery of nutraceutical ingredients in structures such as nanoparticles, fibrils, nanotubes and micelles. Its functional properties can be increased by

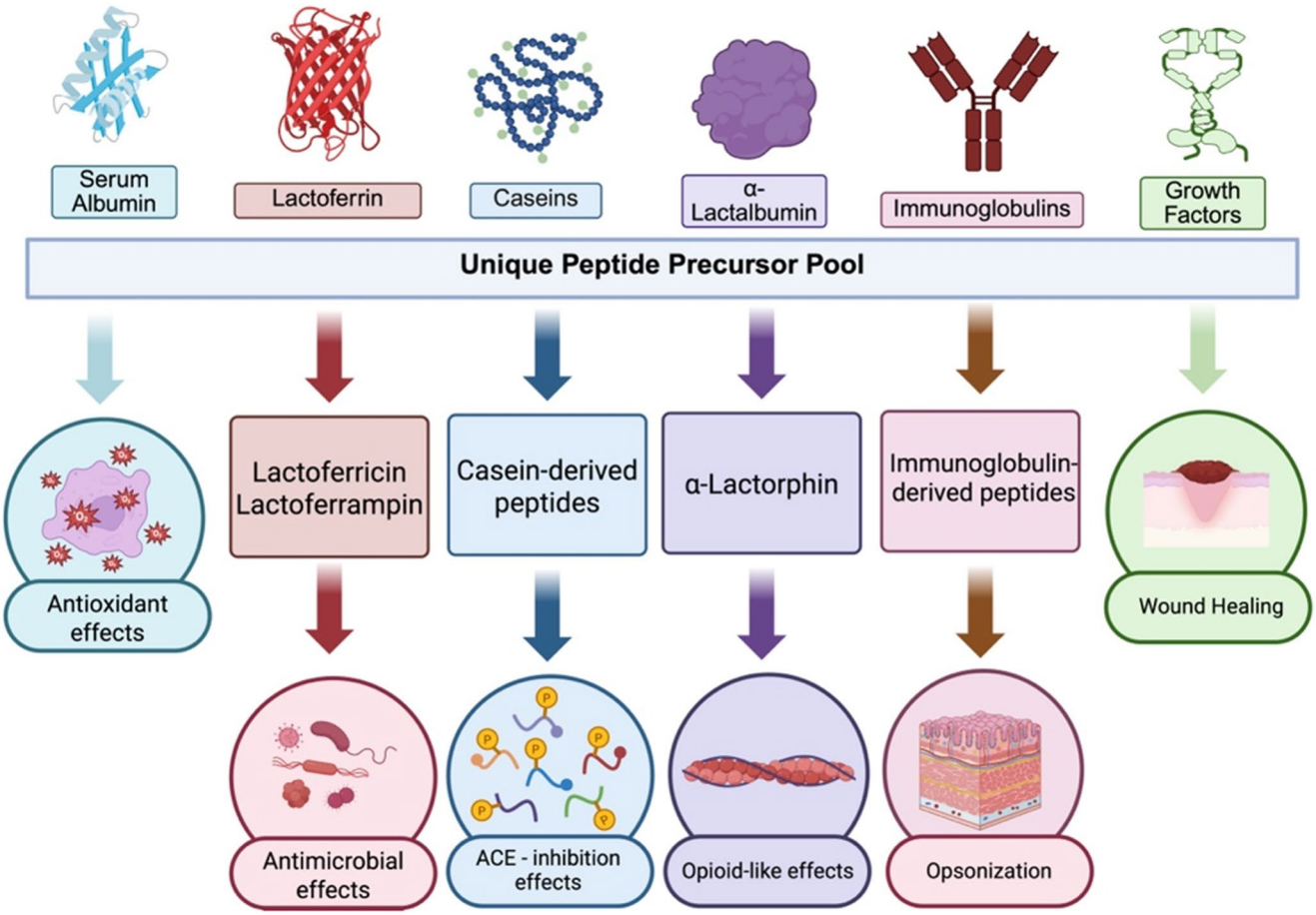


Fig. 1 Multimodal effects of major proteins and their bioactive peptides in BC

various modification techniques such as methods such as heating, ultrasound-assisted glycation, pH regulation, high hydrostatic pressure application, and ultraviolet light treatment, enzymatic cross-linking and pulse electric fields [42]. α-La also draws attention with its antimicrobial potential; In various studies, it has shown inhibitory effects against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Streptococcus mutans*, *Klebsiella pneumoniae*, *Candida albicans* and some fungal species [43–45]. These effects are attributed to specific peptides formed by the digestion of α-La and gaining structural stability due to four disulfide bridges. These peptides may contribute to the prevention of infections by preventing enteropathogenic bacteria from adhering to intestinal cells. It is also reported that α-La disrupts bacterial membranes, causes cell death, and inhibits protein synthesis and DNA replication. With all these properties, α-La; It is considered a biocompatible and safe bioactive protein with broad potential in the fields of food, medicine and especially functional foods [46].

Serum Albumin

Serum albumin, which is a liver originated macro molecule, is a globular protein that has extraordinary stability and is characterized with its acidic structure and high solubility. This structure, which is the most dominant protein compound, plays a role as a dynamic molecular platform in transportation of numerous endogenous and exogenous ligands [47, 48]. Serum albumin functions as a critical redox modulator thanks to its thiol group that is in its structure. This protein participates in biotransformation of xenobiotics by its pseudo-enzymatic activity. Thus, it plays an active role in reducing oxidative stress and regulating toxicokinetic processes [49]. Serum albumin clearly differs from other plasma proteins due to its non-glycosylated molecular structure. This protein forms part of a specialized transportation system that is protected in evolutionary processes, by sharing the same gene family with α-fetoprotein, vitamin D binding protein and afamin. The synthesis of albumin starts in the form of preproalbumin which is a precursor molecule. This polypeptide chain gains functional conformation by a range of post-translational modifications. The primary structure of serum albumin represents variation between species. This case directly affects the total amino acid sequence of the protein. For instance, bovine serum albumin (BSA) contains 584 residues whereas rat serum albumin contains 583 and differs in terms of molecular level. These sequential differences between species play a determinant role in ligand binding capacity of the protein and immunological response profile [48]. BSA is a single chain biomacromolecule of 68 kDa which has high solubility. Its structure that is rich in carboxyl and amino groups provides flexibility for molecular cross-binding and modifications. These functional groups enhance the usage of this protein in food matrices and also biotechnological systems as a stabilizer agent [50]. BSA is accepted as an equivalent of human serum albumin (HSA) due to its high level of structural homology. This conformational similarity makes BSA an ideal and reliable model protein in biomedical research and ligand attraction studies.

BSA presence in BC is a critical biomarker for integrity of blood-milk barrier and coordination of transition between lactogenesis phases. The concentration of this serum protein provides fundamental physiological data about permeability of breast epithelial tissue and beginning of mature milk secretion. BSA may also be involved in the transport of IgG subtypes present in colostrum, since colostrum is predominantly of the IgG1 isotype and transcytosis mechanisms are involved in the transfer of these Igs from serum to colostrum [51]. From an industrial point of view, BSA is widely used due to its easy availability, low cost and being a by-product of the cattle industry. BSA is preferred in many analysis methods such as immunohistochemistry, ELISA and Western blot due to its biochemically inert structure, and BSA fibers obtained by electrospinning method are biodegradable, biocompatible and biomechanically promising [50, 52]. Especially in applications such as diabetic wound healing, BSA-based biomaterials can support the formation of new vessels [52].

Growth Factors

Growth factors are specific polypeptide structured signal effectors that modulate cellular proliferation, differentiation and tissue regeneration. These molecules, which show function around the local microenvironment via paracrine or autocrine pathways, act as a central regulator in regulation of immune response and maintaining tissue homeostasis [7]. Growth factors such as IGF-I IGF-II, TGF-β, EGF, Platelet-Derived growth factor (PDGF), Vascular Endothelial growth factor (VEGF) and Milk Fat Globule-EGF 8 (MFG-E8) activate cellular signaling cascades through interaction with specific surface receptors, leading to the regulation of gene expression and cellular functions [4].

BC represents a complex biological matrix via its high concentrated growth factor profile including approximately 50 different polypeptide compounds. This rich polypeptide diversity provides the molecular basis of the versatile stimulator effect of colostrum on neonatal development and capacity of specific signalization. These factors are found at much higher levels in colostrum compared to mature milk and because of these properties, BC is considered as a supplement with therapeutic potential [17]. Several studies have shown that growth factors derived from colostrum or milk show positive effects in clinical situations such as disease management and tissue

healing [4]. These biological compounds can largely maintain their stability during processing thanks to their resistance to temperatures up to 60 °C. However, the concentration of growth factors can vary both between species and between individuals of the same species, and a marked decrease in their levels in colostrum has been reported to occur in the first 48–72 h postpartum [17].

Therefore, various new technologies are being developed to efficiently obtain and preserve growth factors and the use of BC in biopharmaceutical applications is increasing.

Insulin-Like Growth Factor

The IGF system composed of IGF-I and IGF-II is a fundamental peptide group that administers cellular homeostasis and survival processes. Thanks to its insulin-like molecular architecture, it coordinates growth and differentiation processes in developmental phases by triggering signal transduction via specific receptors [4]. IGFs trigger PI3K/Akt and MAPK signal cascades via binding specific surface receptors. This molecular interaction forms a strong anti-apoptotic that maximizes cellular survival. Signaling pathways that are mentioned, structure the biochemical basis of rapid neoplasm and cellular adaptation processes [53]. Complete sequence identity between bovine and human IGFs allows these proteins to function as molecular equivalents at the receptor level. Especially in supra-physiological levels, the cross-reaction of these peptides with insulin signaling pathways clarify metabolic regulation power of colostrum in neonatal phase [7]. IGF-I that is produced under the control of growth hormone in the liver, is a strong anabolic effector that administers systemic growth processes. This molecule plays a central role in tissue regeneration and maintenance of metabolic balance in neonatal development phases. BC, which contains IGF-I 25 times more compared to human colostrum (500 mg/L vs. 18 mg/L), represents a supra-physiological growth stimulant for rapid tissue maturation in a newborn. The decline of this high concentration to basal levels in mature milk is a reflection of temporal regulation of growth factor secretion profiles [7]. In BC, IGFs are present in both free and bound forms; the free form is biologically active and triggers cell proliferation, while binding proteins stabilize IGF and reduce proteolytic degradation. It has also been reported that there may be an interaction between IGF levels and gut microbiota. The high IGF content in BC has therapeutic potential, especially in local gut repair and anabolism [4, 7].

Epidermal Growth Factor

EGF, which has a compact structure including 53 amino acids, is a potent mitogenic peptide which regulates cellular proliferation and tissue regeneration thanks to its high affinity interaction with EGF receptor (EGFR). This ligand-receptor complex acts as a central regulator in wound healing and protection of epithelial integrity by activating intracellular signaling cascades [4, 7]. EGF represents a multimodal regenerative effect on epithelium, fibroblast and endothelial cells which are found on different tissue layers. This peptide administers complex wound healing mechanisms by coordinating angiogenesis, collagen synthesis and re-epithelialisation processes [54]. EGF, which is found at high levels in human colostrum, is partially resistant to digestion and promotes local repair by reaching basolateral receptors in the immature intestine. While it has no systemic effect in the intact intestine, it stimulates healing by functioning as a "luminal surveillance peptide" in damaged areas [7]. With these properties, colostrum-derived EGF is an important component in neonatal intestinal development and protection against infections.

Transforming Growth Factor - *β*

TGF-β, which exhibits pleiotropic effects via three different isoforms (β1, β2, β3), represents a central cytokine network in maintaining cellular homeostasis. This molecule plays a critical role as a regulator in cell cycle control and tissue regeneration processes simultaneously whereas modulating immune response via immunosuppressive activity [7]. It is synthesized intracellularly as precursor proteins, complexed with latent associated peptide (LAP) and converted into an active form through interaction with proteases or integrins and binds to TGF-β receptors. This binding triggers phosphorylation of Smad proteins and initiates signaling pathways that regulate gene expression [4]. The TGF-β family is often known for its suppressive effect on cell proliferation, particularly in the gastrointestinal surface epithelium, where it is involved in processes such as neutrophil chemotaxis, epithelial cell migration and wound healing. BC forms a biochemical protective shield for gastrointestinal systems thanks to its high TGF-β concentration in 20–40 mg/L level. This amount satisfies the threshold which is required for stabilizing structural integrity of gut mucosa and repressing local inflammation via inhibiting pro-inflammatory cytokine cascades. From this aspect, BC functions as an active immunomodulator for maintaining neonatal gut homeostasis [7]. TGF-β creates a dynamic balance between immunity effectors and microbiota composition so as to provide gut homeostasis. This cytokine reduces mucosal permeability by regulating tight junction proteins of the gut epithelial barrier. Simultaneously, thanks to its immunomodulatory activity, it leads to development of immune tolerance in newborn's gut lumen by repressing local inflammatory responses [7, 17, 55]. By regulating both adaptive and innate immune responses, this cytokine supports immune system development in early life and helps reduce the risk of allergies and inflammation [17, 55].

Platelet-Derived Growth Factor

PDGF, secreted from different cell types, especially platelet α-granules, is a disulphide-binded dimer which exhibits a strong proliferative effect on fibroblasts of mesenchymal origin and smooth muscle cells. PDGF, thanks to its ability of exhibiting high stability against acidic gastric environment, stimulates tissue regeneration and angiogenesis by protecting its biological activity in gastrointestinal system when taken orally [7, 56]. In preclinical models, this growth factor has been shown to play a critical role in mucosal barrier repair through macrophage activation and accelerated ulcer healing [7].

Vascular Endothelial Growth Factor

A heparin-binding homodimer, VEGF (34–42 kDa) is a primary signaling molecule that administers angiogenesis and microvascular permeability via specific receptors on vascular endothelial. This glycoprotein optimizes blood flow and nutrition support by enhancing local vascularisation in gut lumen, which is required for epithelial repair. In mucosal damage cases, especially peptic ulceration, neovascularisation, which is induced by VEGF, is a critical factor that speeds up regeneration cascade by stabilizing tissue perfusion [7, 57].

Milk Fat Globule Epidermal Growth Factor 8

Lactadherin (MFG-E8) is a versatile glycoprotein present in high concentration in BC beyond being a structural compound of milk fat globule membrane. This molecule plays a critical role in tissue homeostasis by coordinating removal of damaged and apoptotic cells via phagocytosis. Also it stimulates angiogenesis via VEGF-dependent signaling pathways and supports integrity of gastrointestinal barrier by triggering epithelial regeneration [7, 58].

Enzymatic Release and Peptide Generation

According to the results of one study, bovine Lf (bLf) remained relatively more intact during the digestive process compared to human Lf. Specific therapeutic peptides were released after peptide digestion, especially in the gastric phase. Digestion followed the INFOGEST protocol using simulated fluids. After 120 min, pepsin was inactivated, and intestinal digestion began Western blot, SDS-PAGE and ELISA analyses show that human milk Lf (hmLF) and recombinant human Lf (rhLF) show some durability in the gastric phase but are largely degraded after intestinal digestion. For each LF type, peptidomic analysis identified distinct peptide profiles at different digestion stages. All types—bLF, hmLF, and rhLF—displayed a comparable pattern, with peptide release peaking during the gastric phase and declining in the intestinal phase. This indicates the pivotal role of the gastric environment in facilitating bioactive peptide release [59]. Both intact Lf and its digestion-derived peptides exhibit multiple bioactivities, including antimicrobial, ACE-inhibitory, and DPP-IV-inhibitory effects. As whey proteins pass through the gastrointestinal tract, they are hydrolyzed by gastric pepsin and pancreatic enzymes, resulting in the release of bioactive sequences encoded within the original protein structure. These peptides may demonstrate a range of physiological functions at target sites, including antimicrobial, antioxidant, antihypertensive, hypocholesterolemic, and anticancer activities. Although in vivo digestion in humans provides the most physiologically relevant data, in vitro digestion systems represent a practical alternative due to their cost-effectiveness, reproducibility, and ethical advantages [59].

In vitro gastric and intestinal digestion performed on WPI followed compatible INFOGEST protocols. In simulated intestinal digestion, the chymus was neutralized to pH 7.0, bovine bile and porcine pancreatin solution with 100 U/mL trypsin activity were added and incubated at 37 °C. In this process, 25 bioactive peptides remained stable throughout the gastric and intestinal phase. These peptides were derived from β-casein, BLG, ALA and κ-casein proteins and showed various activities such as antimicrobial, ACE inhibitor and DPP-IV inhibitor. In studies conducted under static in vitro conditions and in three adult individuals, 1187 gastric, 449 intestinal and 1041 jejunal unique peptides were identified by LC-MS/MS; 61 of these were shown to have bioactive properties [60]. The production of peptides exhibiting antimicrobial, antioxidant, and opioid properties reveals therapeutic potentials that may support gut health.

Furthermore, EndoBI-1 from *Bifidobacterium longum* subsp. *infantis* cleaves *N*-glycans without denaturation and is tolerant to fucosylation. Thus, the biological effects of glycans on the structure-function relationships of proteins can be evaluated by preserving their natural forms. Glycans influence protein folding, solubility, immune response, and resistance to digestion. EndoBI-1 allows selective glycan analysis under different conditions. N-linked glycosylation has been implicated in the protection of human and bovine Lf against proteases such as trypsin and chymotrypsin, while human apoLf has been reported to be unusually resistant to proteolytic digestion [29].

Key Colostrum-Derived Peptides and their Activities

Unlike peptides which are determined in conventional milk systems, significant abundance of bioactive precursors in colostrum changes the dynamics of peptide production radically. Specific constituents of colostrum, such as Lf and active immunological compounds, reidentify functional importance of peptides which are derived from this source.

Lactoferrin-Derived Peptides

Lactoferricin

Lactoferricin is the first peptide derived from Lf by enzymatic hydrolysis with pepsin and was first isolated from bovine Lf by Tomita et al. in 1991 [61]. This peptide is derived from the N-terminal region of the Lf molecule from a 25 amino acid sequence corresponding to amino acid residues 17–41 in bovine Lf [61–63]. Lactoferricin obtained from digestion under acidic conditions (pH 2–3) and high temperatures (100–120 °C) exhibited stronger antibacterial properties than full-length lactoferricin in most cases [61]. Bovine lactoferricin has a cyclic structure with higher antimicrobial activity compared to its linear form, which allows it to penetrate the double layer of the bacterial membrane more efficiently and form more stable bonds with negatively charged membrane regions [64]. Crystallographic and nuclear magnetic resonance studies revealed that in aqueous solution bovine lactoferricin folds into a hairpin-like amphipathic structure containing two antiparallel β-strands and an intramolecular disulfide bond [61, 63]. In contrast, the 49-amino acid sequence that makes up human lactoferricin is a continuous chain stabilized by two disulfide bonds, showing an irregular structure in aqueous solution but acquiring α-helical tendency in membrane-mimetic environments [61, 63]. Both bovine lactoferricin and human lactoferricin adopt amphipathic conformations with a marked distinction between hydrophobic regions represented by tryptophan residues and positively charged hydrophilic regions represented by arginine residues [62, 63]. This property makes them effective antimicrobial and antitumor agents capable of selectively interacting with negatively charged surfaces of Gram-positive and Gram-negative bacteria, fungi, parasites, viruses and tumor cells [61, 63]. Studies have shown that even shorter segments of bovine lactoferricin, such as residues 17–31, can exert significant antibacterial activity and that the 11-amino acid portion at positions 20–30 is critical for this effect; cyclization of this region further enhances antimicrobial activity [61–63]. Furthermore, lactoferricin has been reported to exert antitumor effects against many tumor cell lines, including leukemic cells, fibrosarcomas, melanomas and colon carcinomas, without toxic effects on normal fibroblasts and erythrocytes [63]. This selectivity is explained by its specific binding to negatively charged phospholipids, such as phosphatidylserine, which is released as a result of the disruption of phospholipid asymmetry that occurs in diseased cell membranes. Following binding, lactoferricin is thought to disrupt the cell membrane and trigger cell death via a calcium/magnesium-dependent endonucleases and oxidant-mediated apoptotic pathway [65]. In conclusion, lactoferricin stands out as one of the most important bioactive peptides derived from BC, not only retaining many of the biological functions of lactoferricin, but also showing higher levels of antimicrobial and antitumor activity.

Lactoferrampin is a cationic antimicrobial peptide derived from bovine Lf that exhibits strong membrane-disrupting and antimicrobial activity without causing hemolysis at effective concentrations [61, 63, 66]. It adopts an amphipathic α-helical structure at its N-terminal end in membrane-mimicking environments, while its cationic C-terminal region, though structurally disordered, plays a crucial role in targeting microbial membranes by electrostatically interacting with negatively charged surfaces [67]. Moreover, lactoferrampin may interfere with viral envelopes or capsids by binding to their negatively charged components, disrupting structural integrity and lowering infectivity [68].

Lactoferrampin

Lactoferrampin is one of the additional bioactive peptides derived from Lf and was first identified from bovine Lf and chemically synthesized in 2004 [63]. Like lactoferricin, lactoferrampin is derived from the cationic N-lobe of Lf, specifically amino acid residues 268–284 in bovine Lf, and has antibacterial and antifungal properties, as shown in Fig. 2 [61, 63, 66]. In 2005, the same research group identified a slightly extended version of this sequence, a more potent peptide containing residues 265–284. Bearing structural features common to antimicrobial peptides, lactoferrampin adopts an amphipathic α-helical conformation at the N-terminal end in membrane-like solvents, while the cationic C-terminal part, critical for antimicrobial activity, generally remains disordered [63]. This feature plays a role in the binding of the peptide to target cell membranes. Although the synthesized lactoferrampin peptide shows activity against a wide range of bacteria, including *Porphyromonas gingivalis*, *Actinomyces naeslundii*, *S. mutans* and *Streptococcus sanguis*, resistance to some strains has also been observed [61, 66]. Notably, however, it does not show hemolytic activity at antimicrobial effective concentrations [62]. In silico analysis using ExPASy Proteomics Server revealed that lactoferrampin and three different peptide segments (f(259–284), f(265–296) and f(265–284)) can be obtained from bovine Lf with site-specific endoproteinases such as ArgC and AgrN, and all of these peptides showed antibacterial activity against *E. coli* [61, 66]. Furthermore, human lactoferrampin corresponding to residues 269–285 was synthesized as a homologue of bovine lactoferrampin, but this version was ineffective against *E. coli* and *S. sanguis*; antimicrobial activity was gained only with some modifications in the sequence [61]. This molecule, which has the typical characteristics of antimicrobial peptides, shows a broad

spectrum of activity thanks to the positively charged residues in the N1 domain and the hydrophobic region containing tryptophan, and is noteworthy in clinical applications for its lack of hemolytic activity [63]. Transmission electron microscopy analysis of bovine lactoferrampin-treated *E. coli* and *C. albicans* cells showed that the peptide caused partial disruption of the plasma membrane and therefore the primary target of lactoferrampin was the cytoplasmic membrane [67]. Structurally, lactoferrampin is unstructured in aqueous media, whereas in the presence of lipids it acquires an α-helical structure and exhibits an amphipathic helix character in the N-terminal region in SDS micelle-bound NMR analyses. In contrast, the cationic C-terminal region does not contain any obvious secondary structure, but the positive charge content of this region directly affects the intensity of antimicrobial activity; removal of charges in this region decreases the activity, while addition increases it [67]. Based on these data, the antimicrobial effect of lactoferrampin is thought to be mediated by electrostatic attraction of the cationic C-terminus to negative charges on the bacterial surface, followed by burial of the N-terminal helix in the bilayer, leading to membrane disruption [62]. It has also been suggested that lactoferrampin may disrupt the viral envelope, as shown in Fig. 2., preventing virus binding and entry into the host cell; positively charged residues interact with negatively charged components of the viral envelope or capsid, weakening the structural integrity of the virus and reducing its infectivity [68].

Casein-Derived Peptides

Beyond their well-known nutritional role, caseins constitute a reservoir of encoded bioactive peptides with significant biological potential. These casein-derived peptides (CDPs) are of increasing scientific interest due to their broad spectrum of bioactivities that can provide beneficial effects on both human and animal health. Numerous physiological functions have been attributed to these peptides, including antimicrobial, antihypertensive, opioid-like and immunomodulatory effects [69]. The diversity of these biological effects is due to specific amino acid sequences in the major casein proteins which upon enzymatic release can interact with different molecular targets in the organism [69, 70]. In terms of cardiovascular health, some CDPs, such as casokinins, exhibit ACE inhibitory effects that help regulate blood pressure. This mechanism is similar to some

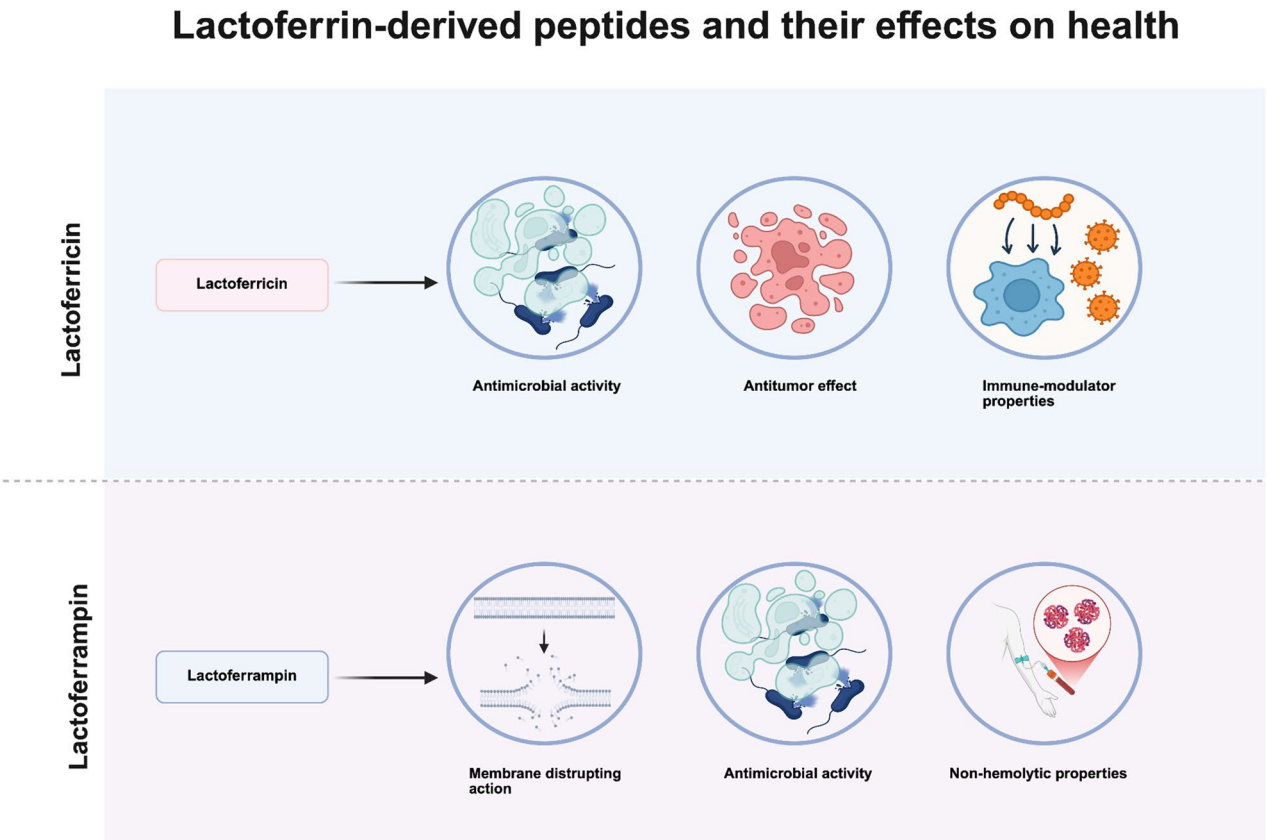


Fig. 2 Lactoferrin-derived peptides and their effects on health. Lactoferricin, exhibits potent antimicrobial and antitumor properties, making it one of the most functionally significant bioactive peptides derived from BC. Through these multifaceted mechanisms, lactoferricin contributes not only to host defense but also to potential immunomodulatory and anticancer therapies

antihypertensive drugs but offers a natural, food-based intervention. With lifestyle-related hypertension on the rise, CDPs offer a potential dietary approach to manage blood pressure [69]. The milk bioactive peptides database contains 355 ACE inhibitory peptides and 5 antihypertensive peptides. These peptides are mainly derived from β-casein, αs1-casein and β-lactoglobulin [70].

Liu et al. [71] demonstrated that the β-casein derivative LLYQEPVLGPVR had potent in vitro ACE inhibition, was highly stable throughout simulated gastric digestion, and the shorter peptide fragments produced after simulated intestinal digestion showed higher ACE inhibitory activity than the full peptide sequence. Of the two ACE inhibitory peptides derived from the enzymatic hydrolysis of yak milk β-casein (PFPGPIPN and LPLPLL), PFPGPIPN was stable throughout gastrointestinal digestion in vitro, whereas LPLPLLL was cleaved to the known ACE inhibitory peptide PLP. Oral administration of the bovine αs2-casein peptide YQKFPQYLQY to spontaneously hypertensive rats significantly reduced blood pressure [70]. Casein-derived inhibitors of ACE are called casokinins. Casokinin sequences have been found in αS1-, β- and κ-casein. Structure-activity correlations between different peptide inhibitors of ACE show that binding to ACE is strongly influenced by the C-terminal tripeptide sequence [72]. In addition, CDPs such as β-casomorphins interact with opioid receptors, causing mild analgesic and sedative effects [69].

Opioid peptides are peptides known to bind to and activate or inhibit opioid receptors μ, κ and δ. Opioid receptors are found in the nervous, endocrine, immune and gastrointestinal systems of mammals. Opioid peptides derived from milk play both agonistic and antagonistic roles. Two important effects that opioid peptides may have on the gut are modulation of peristalsis and mucus secretion [70]. Common structural features of both exogenous and endogenous opioid peptides are the presence of a tyrosine residue at the N-terminus and another aromatic residue such as phenylalanine or tyrosine at the third or fourth position. A total of 26 unique peptide sequences with opioid activity derived from milk proteins have been identified. Twenty-one peptides have been identified from cow's milk proteins, including caseins, β-lactoglobulin and Lf. Casomorphin-7 (YFPPGPI from bovine β-casein) has opioid activity [70]. β-Casomorphin-7 (BCM-7) is a peptide released through proteolysis of β-casein, which is considered to be a bioactive peptide showing evidence that it promotes binding and activation of the μ-opioid receptor found in various parts of the body such as the gastrointestinal tract, immune system and potentially the central nervous system. The major potential agonist effect of BCM-7 is modulation of motility, which delays gastrointestinal transit time and increases mucus production in humans [73]. BCM-7 can penetrate the gastrointestinal wall and enter the bloodstream. BCM-7 is a pro-inflammatory exogenous (food protein) opioid peptide. BCM-7 has been linked to the oxidation of human LDL (low-density lipoprotein), a risk factor for heart disease. BCM-7 promotes LDL oxidation in individuals at risk of heart disease. The BCM-9 peptide shows opioid properties compared to BCM-7, but its binding affinity for μ-opioid receptors is about a quarter that of BCM-7 [74].

Proline-Rich Peptides

PRPs are polypeptides with molecular weights ranging from 0.5 to 17 kDa, containing highly hydrophobic amino acids (~45%) and more than 20% proline. These PRPs originate mostly from caseins such as β-casein and α-casein, with colostrum being the only known source of PRPs. First isolated from sheep colostrum in 1974, PRPs were later identified with similar sequences in goat, bovine and human colostrum [75]. PRPs support the weakened immune system and help regulate it by stimulating the thymus gland, which produces T cells [76]. They also support immune defenses in autoimmune disorders and soften the extreme reactions that define these disorders by preventing the overproduction of T cells and lymphocytes, thus reducing pain and swelling [76, 77]. PRPs can stimulate cytokine production, growth and differentiation of B cells, as well as natural killer cell activity [78]. PRPs extracted from colostrum have been shown to have multifaceted effects such as immunomodulatory effects, support of cognitive functions and prevention of pathological processes in the central nervous system [75]. PRPs, which have physiological benefits such as increasing insulin production, inhibiting tumor growth and strengthening general immunity, show beneficial effects in Alzheimer's disease (AD) and exhibit procognitive and immunomodulatory properties by regulating upstream processes associated with inflammation, brain aging and neurodegeneration [75, 79, 80]. In this context, colostrin, a proline-rich peptide, is reported to be a potential agent for the treatment of neurodegenerative and autoimmune diseases [77].

α-Lactalbumin Peptides

α-Lactorphin (Tyr-Gly-Leu-Phe) is a tetrapeptide released in amidated form from amino acid residues 50–53 or 69–72 of α-La, one of the whey proteins in milk, and is classified as a food-derived exorphin [81–83]. This peptide is released during enzymatic proteolysis of α-La by gastric and pancreatic enzymes under in vitro conditions and can be obtained in yields of up to 39 mg from approximately 1 gram of α-La protein [81, 84]. α-Lactorphin binds to μ-opioid receptors and exhibits agonist effects and opioid-like activities [82, 83]. This peptide has been shown to exert favorable effects

on endothelial function and enhance endothelium-dependent vasorelaxation in rat mesenteric arteries via a nitric oxide-mediated mechanism [81]. In subcutaneous administration, it showed antihypertensive effects by lowering blood pressure in both normotensive Wistar Kyoto rats and spontaneously hypertensive (SHR) rats, which could be abolished by opioid receptor antagonist [81, 84]. However, no sedation or antinociception, the classic central opioid effects, were observed in behavioral tests in intraperitoneally administered mice [81]. Furthermore, α-lactorphin plays a potential role in the maintenance of mucosal immunity by increasing mucin gene expression [83]. Through these multifunctional effects, it is suggested that dairy products containing α-lactorphin may have beneficial effects on cardiovascular health.

In this context, since the number, scope and timeliness of studies on specific bioactive peptides such as α-lactorphin are limited in the current literature, there is a need for more in-depth and targeted research in this field. This deficiency provides an opportunity to better understand the molecular mechanisms and to develop original research articles that will pave the way for the next generation of functional food and pharmaceutical applications.

Immunoglobulin-Derived Peptides

The structure of Igs perfectly fits their transforming function: bipolar molecules have variable regions to recognize the diversity of antigenic epitopes and have several different constant regions that mediate their effector function [85]. Igs are composed of two F(ab) fragments and an Fc fragment with distinct properties [39, 86]. An antibody has two identical F(ab) fragments (50 kDa) that contain the entire light chain and the variable and first constant domain of the heavy chain and are responsible for antigen binding. Antibody digestion with papain produces two monovalent F(ab) fragments with only one antigen binding site. The Fc fragment (50 kDa) consists of the heavy chain constant region of an antibody. The Fc fragment binds to endogenous Fc receptors on the surfaces of immune cells and thus mediates the effector functions of an antibody. IgM is produced before class switching and somatic hypermutation and has a low affinity [39]. However, the secreted pentameric form provides 10 antigen binding sites and thus has an overall high avidity IgM is particularly effective in activating the classical complement system leading to opsonization of antigens and cytolysis. IgA antibodies are monomeric in serum or secreted in the mucosa as dimers bound by a linker peptide. Because of its localization on mucosal surfaces, IgA usually provides the primary defense mechanism against infections, either through direct neutralization or by preventing adhesion and penetration of epithelial surfaces. IgA is transported to mucosal surfaces via pIgR in polymeric form, where it provides barrier function by preventing pathogen binding (Table 2) [39].

Ig-based peptides originate from different regions of the immune system and can exert various effects on human health. Fc-peptides are derived from the Fc region of Igs and are particularly used in drug delivery therapies for certain diseases [91]. F(ab')$_2$ fragments are obtained from the Fab regions of Igs and provide passive immunity by specifically binding to and neutralizing toxins. This structure is widely used as a therapeutic agent, especially in antivenom treatments [92]. SC-peptides (secretory component), as part of SIgA, play an important role in maintaining mucosal immunity by protecting Igs from degradation in enzymatically challenging environments such as the stomach, thereby preserving their functional integrity [93]. Colostrinin™, a PRP complex derived from BC, exhibits strong immunoregulatory and neuroprotective effects by modulating cytokine responses. It has shown promising results in the treatment of neurodegenerative diseases such as AD disease [94]. These findings indicate that Ig-derived peptides not only support the immune system but also possess a wide range of biofunctional applications for therapeutic purposes.

Peptides, which are firstly characterized in milk-derived systems, play a more dominant biological role in this special secretion due to their high presence of precursor in early colostrum phases. Thus, specific compounds of colostrum require these peptides to be evaluated in a specifically biochemical context independent of milk systems.

Biomedical Applications

Bioactive peptides derived from BC, as mentioned in the previous sections, are of increasing interest not only in the clinical therapeutic field but also in biomedical applications, which are expanding across different disciplines, thanks to their antimicrobial, immunomodulatory, anti-inflammatory and cell regeneration-promoting properties. These peptides

Table 2 Ig-derived peptides and their functions on the body

Peptide	Source	Function	Reference
Fc-peptides	Fc region of Ig	Drug-delivery therapeutics for certain diseases.	[87]
F(ab')$_2$	Fab region of Ig	Provides passive immunity by specifically binding to and neutralizing toxins.	[88]
SC-peptides (secretory component)	Secretory IgA	Contribute to mucosal immunity by protecting Igs from enzymatic degradation.	[89]
Colostrinin	BC	Exerts neuroprotective and immunoregulatory effects by modulating cytokine responses.	[90]

are used in functional supplements to support the immune system, prevent exercise-induced mucosal damage and accelerate recovery, especially in the protection of athlete health; and in antimicrobial coating technologies, they contribute to food and medical surface safety by forming natural, non-toxic barriers. In addition, they are used as peptide components that support cardiovascular, metabolic and intestinal health in the formulations of nutraceutical and functional food products; they are among the promising natural agents for biological wound healing and regenerative medicine applications by supporting healing processes such as epithelial proliferation, collagen synthesis and local inflammation control in the field of tissue regeneration by balancing pro- and antiinflammatory cytokine responses in the modulation of the immune system. This multidimensional effect makes colostrum-derived peptides an important component of both traditional and innovative biomedical solutions as a result of various in vitro and in vivo studies.

Acute Diarrhea

Antimicrobial, barrier protective and immunomodulatory spectrum of BC-derived peptides offers a critical mechanistic ground to investigate roles of these biomolecules in acute diarrhea pathophysiology. These peptides, by their versatile effect mechanisms such as; inhibition of enteropathogenic microorganisms, regulation of intestinal inflammation and restoration of epithelial integrity, have the potential of minimizing clinical severity and duration. A double-blind, randomized controlled trial involving 160 children with acute diarrhea evaluated the effect of BC-derived bioactive peptides (Table 3). Participants received either peptides ($n=80$) or placebo ($n=80$). All were tested for common bacterial pathogens and Rotavirus. After 48 h, the BC group showed significantly lower rates of vomiting, diarrhea, and Vesikari scores, regardless of whether the cause was *E. coli* or Rotavirus ($p=0.000$) [95]. BC-derived peptides appear effective for treating acute diarrhea and may help prevent related complications.

Tuberculosis

The membrane-disruptive and immunomodulatory capacity of Lf-derived peptides, open a new therapeutic window into pathogenesis of tuberculosis. Especially the ability of targeting bacteria membrane integrity and coordinating immune response of the host, represent a fundamental rationale for the investigation of the critical role of these molecules in Mycobacterium tuberculosis infections. These mechanistic features support positioning of peptides as potential assistant agents in clinical administration of tuberculosis. In this study, lactoferricin was shown to suppress mycobacterial growth in susceptible, INH-monoresistant, RF-monoresistant and MDR M. tuberculosis strains at 100–200 µg/mL. Similar effects were observed on some atypical mycobacteria. Antibiofilm effect was not significant for M. abscessus. In combination tests, it showed additive effect with INH (FICI: 0.730) and synergistic effect with RF (FICI: 0.312). Doses up to 4 mg/mL were found to be safe with $<1\%$ hemolysis [96]. The results suggest that lactoferricin has potential as adjuvant therapy in both susceptible and resistant TB infections.

Wound Healing

Regenerative and anti-inflammatory capacity, represented by colostrum-derived peptides, prepares an optimized microenvironment for tissue regeneration by combining with their strong antimicrobial activities. The regulatory effects on modulation of cytokine responses, promotion of cellular proliferation and rearrangement of extracellular matrices, feature therapeutic potential of these peptides in wound healing and tissue regeneration processes. Colostrum-derived extracellular vesicles (Colos EVs) promote re-epithelialization, angiogenesis, and extracellular matrix maturation. They remain stable after freeze-drying, retaining their wound-healing properties. In vitro, Colos EVs accelerated wound closure nearly fourfold and were more effective than Milk EVs and recombinant human EGF (rhEGF). They are rich in bioactive molecules, including anti-inflammatory (clusterin, CD5L), regenerative (apolipoprotein E), and structural proteins (PGLYRP, B4GALT1), as well as miRNA-21, whose inhibition reduced their efficacy. These results suggest that Colos EVs are potent, stable agents with therapeutic potential in wound healing [100].

Sport Nutrition

The intestinal integrity stabilization and exercise stress dependent inflammatory response modulation ability of colostrum-derived peptides become a focus in sportsman health research. Immune homeostasis supportive role of these bioactive sequences, offers a mechanistic base in behalf of increasing after training recovery efficiency and enhancing performance outcomes. This study examined the effects of long-term BC-derived peptide supplementation on immune responses to exercise in 27 elite female basketball players. The experimental group received 3.2 g/day of peptides for 24 weeks, while controls received placebo. Blood samples collected before and after exercise at baseline, 3, and 6 months were analyzed. IL-10 and CK MM levels increased post-exercise in the control group but remained stable in the supplemented group. No significant changes were observed in IGF-1 or immune-related blood

Table 3 Table of in vivo and in vitro studies and results of major colostrum proteins and colostrum-derived peptides within the framework of antimicrobial coating, nutraceutical and functional food use, immune support in vulnerable populations, wound healing and tissue regeneration and sports nutrition

Clinical Application	Population	Study Design	Dose	Duration	Results	Reference
Acute Diarrhea	160 children (6 months-2 years) with acute diarrhea.	They were randomly divided into two groups: 80 received BC in addition to standard treatment and 80 received placebo in addition to standard treatment.	1 sachet (3 g; 350 mg IgG, 35.3 mg IgA, 25.3 mg IgM, 65 mg Lf, 2.8 mg lactoperoxidase); dissolved in 50 ml water, on an empty stomach.	1 week	Bioactive peptides reduced the incidence of diarrhea.	[95]
Tuberculosis (TB)	M. TB H37Rv (drug sustainable strain) INH-monoresistance strain RF-monoresistance strain MDR strains *M. abscessus* and some non-tuberculous mycobacteria	In vitro experimental study; antimycobacterial and antibiofilm effects of lactoferricin were evaluated by different assays	100–200 µg/mL (inhibitory concentration range) Tested up to 4 mg/mL in hemolytic test	Variable according to test type; combined effects with biofilm formation and inhibition were studied at different times (specific time not specified)	-Lactoferricin inhibited both susceptible and resistant TB strains -Synergistic effect with RF (FICI: 0.312) -Toxicity was very low (< 1% hemolysis)	[96]
Bovine lactoferricin and MT10 as candidates for intestinal barrier protective and inflammation-reducing therapy in inflammatory bowel diseases (especially enteritis)	Enteritis-induced rats (in vivo) TNF-α-damaged intestinal organoids (in vitro)	Animal study (rat model with enteritis) and in vitro organoid model; mRNA level of inflammation markers and barrier damage analyzed	No specific dose information given; effects were assessed through mRNA expression and organoid stability	Acute experimental period; duration not specified but short-term observation for inflammatory response and barrier analysis	Bovine lactoferricin decreased IL-6, IL-1β, TNF-α mRNA levels NF-κB/NLRP3 pathway inhibited MT10 inhibited TNF-α-induced organoid damage	[97]
Use of bovine lactoferricin as a potential anticancer agent for the treatment of colon cancer (and also prostate and cervical cancer)	Cancer cell lines: Caco-2, HT-29 (colon), DU-145 (prostate), HeLa (cervix) Normal cells: HEK 293, fibroblast, erythrocyte Animal models	In vitro: MTT assay, cell death analysis by cytometry In vivo: Toxicity in Galleria mellonella, zebrafish and CD1 mice	Specific dose ranges are not specified; the most effective peptide (Peptide 3) was synthesized at a scale of approximately 1 gram and applied in various test systems	Cell culture tests: Acute (48–72 h) Short-term observations have been made in animal models (no specific duration given)	Bovine lactoferricin showed potent cytotoxic effect against cancer cells Low toxicity in normal cells and living models Peptide 3 most promising	[98]

Table 3 (continued)

Clinical Application	Population	Study Design	Dose	Duration	Results	Reference
Use of lactoferricin and lactoferrampin and herbal extracts as natural treatment alternatives for the treatment of moderate bacterial and fungal infections	Microorganisms: *S. intermedius*, *Malassezia pachydermatis*, *C. albicans*	In vitro study; interaction of lactoferricin, lactoferrampin and their combinations and natural extracts with MIC (Minimum Inhibitory Concentration) and FIC indices	Peptide and extract concentrations: Determined on the basis of MIC and FIC assays (net values not stated)	Short-term in vitro analysis; effects on cell and microbial growth were measured over incubation periods of several hours	Lactoferricin effective against bacterial species Lactoferrampin effective against fungal species Combination of lactoferricin and lactoferrampin showed synergistic effect Effect enhanced by herbal extracts	[99]
Wound healing	Mice	In vivo, control group	50 µg/per day extravelerated colostrum containing Igs and growth factors for wound healing.	2 weeks	30% faster wound closure, low inflammation	[100]
Mastitis treatment (bovine)	Dairy cows with mastitis	In vivo veterinary practice	Isracidin from β-casein (two doses of 2 g each).	-	90% cure rate; found effective against antibiotic resistant bacteria such as *S. aureus*.	[69]
Systemic infection prevention	Mice	Subcutaneous infection model	Isracidin (single dose, IM injection)	5 months of observation	Mice protected against infection for 5 months; much higher survival rate than control group	[69]
Immune support, muscle recovery	27 elite female basketball players (age 16–19)	Randomized controlled trial (colostrum vs. placebo)	3.2 g/day capsules (≈30 mg α-lactorphin, 0.16 g PRP)	24 weeks	Significant exercise-induced increase in Interleukin-10 (an anti-inflammatory cytokine) was observed ($p=0.01$); no difference in other biomarkers	[101]
Functional food or supplement to support immune balance in the intestinal mucosa	Japanese white rabbits ($n=3$)	Lf given orally	500 mg/kg Lf	3 h later, blood was drawn	Anti-inflammatory cytokines such as IL-10, IL-4 and TGF-β1, which regulate the immune system, increased. Pro-inflammatory cytokines associated with harmful effects, such as IL-1β, TNF-α and IFN-γ, decreased.	[102]
Wound healing, inflammation control, therapeutic use	Japanese white rabbits ($n=3$)	Lf injected into the peritoneum	100 mg/kg Lf	2 h later, blood was drawn	A much more pronounced immunomodulatory response was observed than oral administration.	[102]
Systemic anti-inflammatory use	Japanese white rabbits ($n=3$)	Lf injected intravenously	50 mg/kg Lf	2 h later, blood was drawn	The effects were similar, but milder than with intra-abdominal administration.	[102]
Stimulating the immune system	Japanese white rabbits ($n=3$)	IGF-1 given orally	20 µg/kg IGF-1	3 h later, blood was drawn	Cytokines that activate the immune system such as IL-1β, TNF-α, IL-6, IFN-γ were elevated.	[102]
Stimulation of cellular growth and metabolism	Japanese white rabbits ($n=3$)	IGF-1 injected into the peritoneum	2 µg/kg IGF-1	2 h later, blood was drawn	The strongest pro-inflammatory response was observed.	[102]
Indications for tissue regeneration or muscle growth	Japanese white rabbits ($n=3$)	IGF-1 injected intravenously	2 µg/kg IGF-1	2 h later, blood was drawn	Increase in pro-inflammatory cytokines, at a more moderate level	[102]
Immune stimulating effect	Japanese white rabbits ($n=3$)	IgG given orally	400 mg/kg IgG	3 h later, blood was drawn	Pro-inflammatory response was observed: IL-6, TNF-α, IL-1β increased; suppressors such as IL-10 and TGF-β1 decreased.	[102]

Table 3 (continued)

Clinical Application	Population	Study Design	Dose	Duration	Results	Reference
Therapeutic effects in autoimmune diseases or inflammatory conditions	Japanese white rabbits ($n=3$)	IgG injected into the peritoneum	100 mg/kg IgG	2 h later, blood was drawn	Immunosuppressive (anti-inflammatory) response occurred: Cytokines such as IL-10 and TGF-β1 increased.	[102]
Mechanism of immune regulation similar to clinical antibody therapies	Japanese white rabbits ($n=3$)	IgG injected intravenously	50 mg/kg IgG	2 h later, blood was drawn	Anti-inflammatory response: IL-10 and TGF-β1 increased, IL-6 and TNF-α decreased. The opposite effect of the oral route was observed.	[102]
Anti-inflammatory effect and uterine protective effect	Mice (inflammation induced by lipopolysaccharide during pregnancy)	Different doses of Lf were administered after intraperitoneal injection of lipopolysaccharide.	2.5, 5 and 10 mg/kg (oral bovine Lf)	Acute (short-term follow-up after a single dose)	Dose-dependent histopathological improvement in uterine tissue, decrease in nitric oxide levels, inhibition of proinflammatory markers such as NF-κB (nuclear factor kappa B), TNF-α (tumor necrosis factor alpha) and IL-1β (interleukin-1 beta) were observed. The highest dose (10 mg/kg) gave the best results.	[103]
Neuroprotective effect against prenatal glucocorticoid damage	Pregnant rats given dexamethasone (model mimicking preterm labor)	Maternal rats were supplemented with Lf during pregnancy and lactation. Neurological markers were examined in the offspring in response to glucocorticoid exposure.	Unspecified (but indicated as an oral Lf supplement)	Pregnancy + breastfeeding period	Lf restored the expression of brain-derived neurotrophic factor (BDNF) and divalent metal transporter-1 (DMT-1). It also increased the expression of genes such as Nrep (neuronal regeneration protein) and S100B (marker of glial damage). Glutamatergic dysfunction was prevented. This indicates that maternal Lf can reduce fetal neurological damage.	[103]
Anticancer support: tumor suppression in breast cancer	BALB/c female mice + 4T1 mammary tumor	Tamoxifen and LF were co-administered in preventive and therapeutic models.	Tamoxifen 5 mg/kg bLF: 5 g/kg with feed (oral)	~4 weeks	LF + tamoxifen diet delayed tumor growth by 4 days, reduced tumor size and metastasis. Weight loss was prevented. IFN-γ and IL-18 decline was prevented by LF. LF induced migration of immune cells to the tumor.	[104]
Prevention of HPV-16 entry into the cell	HaCaT cell line (human keratinocytes)	Bovine Lf	35 µg/mL (IC_{50} - concentration required for 50% inhibition)	Short-term cell incubation	LF inhibited the binding and entry of HPV-16 into the host cell in a dose-dependent manner. Maximum inhibition reached 90%. It was more effective at lower concentration than human LF.	[105]
Skin health improvement (psoriasis and acne vulgaris)	Patients with inflammatory skin conditions	Use of bovine Lf supplements (oral powder, capsule, gum, etc.)	Not specified (depends on formulation)	Several weeks to months	Significant reduction in inflammatory lesions and improvement in clinical appearance of skin	[106]
Reduction of skin inflammation	BALB/c mice (ear injection model)	Active *Propionibacterium acnes* injected into both ears; LF injected into right ear; inflammation assessed via histology and IL-8 IHC	LF: 5, 10, 20 µM/L (local injection)	24 h post-injection	LF decreased ear erythema, swelling, and granuloma; reduced IL-8 expression in inflamed tissue	[107]

Table 3 (continued)

Clinical Application	Population	Study Design	Dose	Duration	Results	Reference
Supportive neurocognitive therapy - improving cognitive function and increasing brain-derived neurotrophic factor levels	361 healthy volunteers: −18–24 years (Multitaskers, MT) −25–54 years (Attention Deficit Trait, ADT) −55–75 years (Age-Associated Memory Impairment, AAMI)	Randomized, double-blind, placebo-controlled clinical trial	120 µ/day in lozenge form containing Colostrinin®	For 4 months: −30 days use + 14 days break - in 2 courses	- Brain-derived neurotrophic factor (BDNF) levels in serum increased in 63.1% of participants in the treatment group, but only in 24.7% in the placebo group -Montreal Cognitive Assessment (MoCA) scores significantly increased in the elderly group (up to +5 points in some individuals) - Improvements in Cambridge Neuropsychological Test Automated Battery (CANTAB) subtests across age gro ups: -Delayed Matching to Sample (DMS): Visual memory improved -Paired Associates Learning (PAL): Learning performance increased - Rapid Visual Processing (RVP): Attention span improved -Reaction Time (RTI): Shortened reaction time -No side effects reported	[79]
Candidate peptide for NEC prevention/treatment (LFDP1; Lf-derived peptide)	In vivo: NEC-induced neonatal rat pups In vitro: IEC6 and FHC intestinal epithelial cell lines Validation: Human NEC intestinal tissue samples	Experimental preclinical study (animal model, cell culture, RNA sequencing, human tissue validation)	-	During the NEC induction period	LFDP1 significantly reduced clinical scores and histopathological injury in NEC rat pups. It restored cell viability and enhanced epithelial cell migration and proliferation. It downregulated TLR4, ACSL4, and LPCAT3 expression. It upregulated ZO-1 and GPX4, supporting epithelial barrier integrity. It modulated polyunsaturated fatty acid biosynthesis and fatty acid metabolism pathways. It suppressed ferroptosis by inhibiting the ACSL4–LPCAT3 signaling axis. It reduced oxidative stress and regulated ferroptosis-related protein expression in vitro.	[108]

parameters. In conclusion, BC-derived peptides reduced muscle damage and modulated IL-10 response, but had no major effect on other immune markers [101].

Skin Inflammation

Bioactive peptides which are derived from BC, represent a versatile biological profile that will interfere with pathophysiological processes in skin diseases characterized by inflammation. Regulation of cytokine responses and limitation of microbial colonization capacities of these peptides prepares a steady theoretical ground for enhancing epidermal barrier function and alleviation of chronic irritation. This study showed that Lf reduced IL-8 expression in *P. acnes*-stimulated HaCaT cells and inhibited *TLR2*, NF-κB, and ICAM-1 levels. In mice, *P. acnes*-induced ear inflammation was significantly suppressed by Lf treatment. These findings suggest that Lf may have therapeutic potential against acne-related inflammation [107].

Future research should adopt carrying out the randomized controlled works that have high methodological quality for embodying therapeutic effects which colostrum peptides commit.

Technological and Regulatory Considerations

Although the increasing concern to peptides derived from colostrum, transfer of these compounds to large-scaled and clinical applications are faced with important technological and regulatory obstacles. One of the most fundamental problems is the inability to achieve standardization on a batch-by-batch basis due to its heterogeneous composition that varies depending on lactation phase and individual animal differences. This case makes it difficult to obtain consistent peptide concentration and profile in production processes. Additionally, variable

peptide profiles, which emerged in enzymatic hydrolysis and purification processes, raise difficulties about industrial-scaled reproducibility and quality control. Besides this, the high thermal instability and susceptibility to proteolytic degradation in the gastrointestinal system of BC-derived peptides, create serious limitations about bioavailability and functional efficacy both during processing and after oral application. Common processes such as pasteurization and spray drying prompt to loss of biological activity by degrading tertiary structure of peptides. Even if more sensitive methods can be used such as lyophilization and cold ultrafiltration, these approaches increase cost and an optimized solution that fully guarantees molecular stability throughout its shelf life has not yet been presented. From a regulatory perspective, uncertainty persists regarding the classification of BC-derived peptides as functional food components, nutraceuticals, or pharmaceuticals. The absence of fitted international guides and large-scaled randomized clinical studies, makes assent processes difficult because each every category requires different safety and activity evaluation processes. All these compositional variability, production and stability problems, low bioavailability and failure to fully meet batch-to-batch consistency criteria are the main obstacles to the technological scaling and commercialization of BC-derived peptides. To address these limitations, various delivery technologies have been developed, including nanoformulations, microencapsulation, liposomal carriers, and biopolymer-based systems. For instance, colostrum formulations incorporating protease inhibitors derived from soy have significantly enhanced peptide bioavailability by increasing resistance to digestive enzymes [16]. Additionally, stearin-coated microgranules and multi-layer lipid systems have been found effective in facilitating mucosal transport of growth factors [109]. For example, colostrum peptides that are complexed with β-cyclodextrin decrease bitterness and simultaneously increase antioxidant activity by up to twofold. In addition, encapsulation through complex coacervation using gelatin–gum arabic systems enhances the stability and retention of peptides during transport, particularly in cosmetic and pharmaceutical applications [110].

Comprehensive toxicological data, usage history, and production process documentation are required by the FDA in order for these peptides to obtain GRAS status in the USA. For instance, the colostrum product developed by PanTheryx was recognized as GRAS by an independent expert panel, thereby permitting its use in food and beverage products [111]. In Europe, EFSA considers these components as "Novel Food" and requires a detailed explanation of the production processes, target consumer groups, component characterization, and a comprehensive document including clinical safety data [112]. This demonstrates the critical roles of peptide chemical identifiability, stability, and interactions with delivery systems in regulatory processes. Therefore, technologically advanced delivery systems, such as nanoformulations and encapsulation, not only increase bioavailability but also facilitate the generation of data supporting product safety and efficacy in regulatory approval processes.

Future Perspectives and Challenges

Isolating bioactive peptides from BC from natural sources can be costly and yield limited quantities. Therefore, recombinant DNA technologies can enable the specific production of these peptides in microbial systems (*E. coli*, *Pichia pastoris*). This could support the production of these peptides, which have been clinically validated and have potential effects, as discussed in this review. This production process could significantly simplify sustainability and standardization processes, potentially contributing to the healthcare sector. Furthermore, peptide libraries created by synthetically synthesizing structural variants of these peptides could shed light on the discovery of new molecules with both antimicrobial and therapeutic effects. These synthetic peptides could potentially be made more resilient, targeted, and specific by imparting properties not found in nature.

Colostrum-based bioactive peptides, tailored to an individual's genetic makeup, microbiome, or immune system activity, could play a significant role in the future of functional foods and serve as potential targeted therapies. These peptides can be formulated to meet individual health needs and be utilized as prebiotics, immune boosters, or metabolic regulators. While the biological activities and positive effects of these peptides have yielded very positive results in vitro and in animal models, the literature lacks a sufficient number of randomized, controlled clinical studies in humans. Furthermore, standardization of production costs, shelf life, formulation stability, and regulatory approval processes will significantly impact the future commercial availability of these peptides on the global market.

Conclusion

BC-based bioactives are notable for their richness of content and multifunctional biological effects, and they stand out as highly promising molecules for functional food, pharmaceutical, and clinical applications. These peptides, which have attracted considerable attention with their antimicrobial, antiviral, antiparasitic, anticancer, anti-inflammatory, antioxidant, immunomodulatory, and non-hemolytic properties, possess numerous functional effects, including strengthening the immune system, supporting mucosal defenses, maintaining gastrointestinal health, and positively accelerating tissue regeneration. A growing number of in vitro and animal model studies in the literature indicate that these peptides have broad potential for both prophylactic and therapeutic use. However, several critical challenges remain regarding the introduction of these molecules

into clinical practice. In particular, low oral bioavailability, the risk of enzymatic degradation in the gastrointestinal tract, production standardization, stability issues, and regulatory uncertainties limit the translational transition process. Therefore, the future development of advanced delivery systems (nanoencapsulation, liposomal carriers) to increase the bioavailability of colostrum-derived peptides is crucial. Furthermore, randomized controlled clinical studies in humans should be conducted to thoroughly demonstrate the safety, dosage, mechanism of action, and long-term positive effects of these peptides, and to define standardization requirements. In conclusion, bioactive peptides obtained from BC are biomolecules with high potential that can be used for both preventive and therapeutic purposes. In order to realize this potential, interdisciplinary translational research should be increased and strategies should be developed to facilitate the transition to clinical practice.

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Declarations

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