REVIEW

Supplementation of Bovine Colostrum in Inflammatory Bowel Disease: Benefits and Contraindications

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ABSTRACT

Inflammatory bowel disease (IBD) is a group of chronic relapsing disorders whose etiology has not been fully explained. Therefore, available therapeutic approaches for IBD patients are still insufficient. Current treatment strategies are targeted to immune system dysfunctions, often associated with alternations in the microbiota, which contribute to the development of chronic intestinal inflammation. Therapeutics include anti-inflammatory drugs such as aminosalicylates and corticosteroids, immunosuppressive agents, antibiotics, and biological agents such as infliximab and vedolizumab. Auxiliary therapies involve a balanced and personalized diet, healthy lifestyle, avoiding stress, as well as dietary supplements. In this review, we discuss the use of bovine colostrum (BC) as a therapeutic agent, including its advantages and contraindications. We summarize our knowledge on well-researched BC constituents and their effects on the gastrointestinal tract as evidenced in in vitro and in vivo studies. *Adv Nutr* 2021;12:533–545.

Keywords: bovine colostrum, inflammatory bowel disease, IBD, treatment, gastrointestinal, cytokines, immunoglobulins

Introduction

Inflammatory bowel disease (IBD) refers to chronic relapsing disorders of the gastrointestinal (GI) tract, of which the main 2 are Crohn disease (CD) and ulcerative colitis (UC) (1). The pathogenesis of IBD involves environmental and genetic factors, altered microbiota, and abnormal immune response (2–4). Consequently, current therapeutic strategies are targeted to disturbances in the immune system, which contribute to the development of chronic intestinal inflammation (3). Moreover, recent evidence indicates that IBD pathogenesis can be affected by the food consumed (e.g., a modern Western diet) and a stressful lifestyle (5, 6).

Dysregulated immune response in IBD has been previously correlated with T-helper (Th) 1 cells in CD, and Th2 cells in UC (7), but recent research strongly confirms the role of the IL-23/IL-17 pathway in IBD pathogenesis (8, 9). Activation of Th17 cells, which release IL-17, and altered cross-regulation between Th17 and regulatory T cells appear to be involved in the inflammatory response in the intestines of IBD patients (8). Moreover, abnormal mucosal innate immune responses, associated with defective and increased epithelial barrier integrity, have been highly recognized in IBD (10).

The damage to one of the most important physical barriers in the human body, the intestinal epithelium, which is covered by the mucous layer and is exposed to the external environment (e.g., food antigens or bacteria) may, in turn, lead to intestinal inflammation (11). Dysfunction of the intestinal epithelium is also related to nutrient malabsorption. Apart from this, epithelial cells can also synthesize antimicrobial peptides, and it has been proven that these compounds demonstrate defective expression in CD patients (12, 13).

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Abbreviations used: BC, bovine colostrum; BCM, β-casomorphin; CD, Crohn disease; CMC, colostral mononuclear cell; DSS, dextran sulfate sodium; DUOX, dual oxidase enzyme; EGF, epidermal growth factor; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; GMP, glycomacropeptide; IBD, inflammatory bowel disease; IGF, insulin-like growth factor; LA, lactalbumin; LF, lactoferrin; LPO, lactoperoxidase; LZ, lysozyme; NK, natural killer; PBMC, peripheral blood mononuclear cell; PDGF, platelet-derived growth factor; PRP, proline-rich polypeptide complex; RCT, randomized controlled trial; ROS, reactive oxygen species; SARS-CoV, severe acute respiratory syndrome coronavirus; SC, sodium caseinate; TGF, transforming growth factor; Th, T-helper; TLR, Toll-like receptor; UC, ulcerative colitis; VEGF, vascular endothelial growth factor; α-LA, α-lactalbumin; β-LG, β-lactoglobulin.

Current treatment options for IBD patients include anti-inflammatory drugs, such as aminosalicylates and corticosteroids, immunosuppressive agents (e.g., methotrexate, azathioprine), antibiotics, and biological agents (e.g., infliximab, vedolizumab) (3, 14, 15). Auxiliary therapies involve a healthy lifestyle, balanced and personalized diet, as well as avoiding stress (5, 6). Nevertheless, available therapeutic approaches for IBD patients are still insufficient, which means that future treatment options with novel mechanisms of action are urgently needed.

One of the potential options may be bovine colostrum (BC)—that is, milk produced by female mammals for the first 3 d after parturition, which later changes into mature milk (16). Several investigations confirmed that BC constituents may influence the clinical course of GI, such as IBD (17).

Constituents of Bovine Colostrum

BC is composed of >250 functional constituents, including immune-stimulating peptides and antimicrobial agents (18, 19). Among BC compounds, major ingredients include macronutrients, immunoglobulins, leukocytes, cytokines, growth factors, lactoferrin (LF), lysozyme (LZ), casein, proline-rich polypeptide, glycomacropeptide (GMP), lactalbumin (LA), and enzymes such as lactoperoxidase (LPO) (**Table 1**). Other constituents are vitamins, macro- and microelements, hormones, nucleotides, and gangliosides (20, 21). Colostrum thus contributes to the development of the immune system in infants as well as facilitates growth, maturation, and repair processes in distinct tissues. Consequently, BC has significantly higher amounts of growth-promoting factors compared with mature milk (16, 18, 20).

The contents of bioactive compounds in BC may differ considerably, depending on various factors including lactation number, age of the cow, volume of the first colostrum milking, feeding intensity, exact time after birth, and even season of the year when colostrum is provided to calves (19, 22). The differences may also arise from various cattle breeds and distinct processing methods; for example, calves receiving colostrum within 7 h after birth receive higher amounts of nutrients compared with a group receiving colostrum between 12 and 25 h after parturition (28). Due to the above extensive differences, the majority of constituents in BC cannot be precisely assessed.

TABLE 1 Composition of macronutrients and their derivatives in bovine colostrum

Component	Concentration, g/100 mL	Reference
Total protein	7.1–22.6	(22–24)
Casein	4.8	(24)
Albumin	6.0	(24)
Lactoferrin	0.03–0.21	(22, 23)
Immunoglobulins	5–15	(23–25)
IgA	0.16–0.44	(23, 24, 26)
IgG	3.2–11.33	(23, 24, 26)
IgM	0.43–0.49	(23, 24, 26)
Lactose	2.03–2.5	(23)
Fat	5.35–6.7	(22–24, 27)
SFAs	2.45–3.06	(22–24, 27)
MUFAs	2.35–2.95	(22–24, 27)
PUFAs	0.55–0.69	(22–24, 27)
Choline	0.02–0.04	(27)

Commercially produced colostrum is available in the form of powder, concentrate, lozenges, supplemented milk and beverages, yogurts, butter, and even chewing gums. These forms may differ in compound quality, quantity, and bioavailability (29, 30). Morrill et al. (31) emphasized that almost 60% of colostrum produced on US farms did not meet minimum immunological and bacteriological criteria.

Furthermore, some studies suggest that digestive enzymes may affect colostrum activity, but others indicate that some of its constituents, such as LA or immunoglobulins, are very stable during digestion processes (25, 26, 32). Due to conflicting results, further studies comparing the use of encapsulated and powdered colostrum should be conducted. They might reveal whether BC can survive passage through the GI tract and retain its functionality (33).

Immunoglobulins

BC contains 5 classes of immunoglobulins: IgG, IgA, and IgM, and trace amounts of IgD and IgE that demonstrated a defensive effect against bacteria, viruses, parasites, and fungi (32). The most abundant fractions of immunoglobulins in BC are IgG with predominant subtypes, involving IgG_1 and IgG_2, where the former one accounts for ~75–90% of the total IgG (23–27, 33). The amounts of IgM and IgA are lower, and they significantly dominate in the human body (Table 1). Immunoglobulin concentrations in BC rapidly decrease in the days following parturition.

The primary role of immunoglobulins in the intestine involves binding microorganisms, thereby preventing them from contact with the intestinal epithelium and entering into the bloodstream (34). Immunoglobulins are especially indispensable in ruminants, as their syndesmochorial placenta prevents immunoglobulin transfer into the uterus (35).

It is worth pointing out that heterologous transfer of immunoglobulins from cows to humans appeared to be effective in preventing human diseases. Products prepared from colostrum obtained from hyperimmunized cows, which demonstrated higher levels of immunoglobulins, were used to prevent infectious diseases (36) and treat rheumatoid arthritis, high blood pressure, and oral submucous fibrosis (37).

Leukocytes

BC contains ~10^6 leukocytes/mL (38), and is primarily composed of colostral mononuclear cells (CMCs), such as macrophages and lymphocytes, but also includes polymorphonuclear and epithelial cells (39, 40). It was confirmed that CMCs represent antigen presentation capabilities, and thereby can modulate the immune response, thereby maintaining the equilibrium between immune tolerance and allergy (41). Results of studies on neonatal calves suggested that antigenic and mitogenic stimulation of colostral and

milk lymphocytes was significantly lower compared with blood lymphocytes (42, 43).

Another investigation showed that calves fed live maternal cells (whole colostrum) displayed reinforced reactions to the antigens, which the maternal cow had previously responded to, and not to those to which the maternal cows were naïve (44). The authors stated that maternal vaccination may significantly boost the transfer of appropriate maternal leukocytes in BC.

Another study conducted by the same authors shows that the transfer of maternal colostral leukocytes from whole colostrum affected the development of neonatal lymphocytes, which was reflected by the reinforcement of their antigen-presenting capacity e.g., through positive regulation of major histocompatibility complex (MHC) class I. Moreover, neonate calves fed maternal colostral leukocytes demonstrated reduced expression of markers linked to lymphocyte activation and overall stress compared with calves that received maternal cell-free colostrum (45).

Cytokines

Apart from the cytokines secreted by leukocytes present in colostrum, other cytokines are produced in mammary glands and discharged into colostrum (18, 46). The presence of cytokines in BC is associated with the development of the infant immune system and the ability to regulate the inflammation state (47, 48). Cytokines demonstrate pro-, or anti-inflammatory activity, supporting immunity against viruses, bacteria, or fungi (18, 49, 50). However, available studies show that the concentration of cytokines in BC changes dramatically when cattle becomes infected. In the normal state, cytokines such as IL-1β, IL-6, and TNF-α are usually measured and their concentrations are significantly higher in BC than in mature milk (50).

Growth factors

Primary growth factors present in colostrum include insulin-like growth factor (IGF) 1 and 2, transforming growth factor (TGF) β1 and 2, fibroblast growth factor (FGF) 1 and 2, epidermal growth factor (EGF), β-cellulin (BTC), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). The most abundant growth factors in colostrum are IGF-1 and IGF-2 (51). IGF-1 binds to IGF-1R, IGF-2R, and insulin receptor (IR), whereas IGF-2R bears no structural homology to IR or IGF-1R (52). IGF-1 is responsible for cell growth, proliferation, repair processes, as well as metabolism of macronutrients. Administration of IGF-1 has been widely correlated with growth and repair processes at the level of the gastrointestinal organs as well as anti-inflammatory action (53). With regard to the TGF family, it has been observed that TGF-β1 knockout mice promoted inflammation in different tissues (54). A further analysis linked TGF-β signaling with a wide range of immune-modulating activities and inflammatory responses (54, 55). Investigations focused on EGF have demonstrated its role in stimulating cellular growth (56) and development of intestinal immunity, as well as hampering bacterial translocation (57). PDGF and VEGF were shown to present robust mitogenic activity. The former factor, derivable from platelets and secreted by macrophages, has been observed to be the major stimulator of fibroblasts in colostrum of different species (58).

Lactoferrin

LF is an iron-binding glycoprotein, found in large amounts in several exocrine fluids including milk and colostrum (Table 1). It is commercially available as an extract from bovine milk. Current knowledge about LF is mainly based on its in vivo supplementation in human and mouse models (59, 60).

The biological action of LF include anti-infective, immune-modulating, and either anti- or proinflammatory activity depending on the host immune status (61, 62). It is highly effective against a wide range of viruses and several bacteria, fungi, and protozoa species, and it can modulate intestinal microbiota (63, 64). LF has been also shown to cooperate with lymphocytes, macrophages, granulocytes, and natural killer (NK) cells by influencing their functions (e.g., cytokine production, proliferation, maturation, migration, activation, and cytotoxicity) (63, 65). For instance, LF can reinforce NK-cell activity and the immune response of Th1 cells, and enhance secretion of cytokines preventing viral infection (63).

In viral infections, LF can inhibit the process of virus binding with target cells, especially by impeding its intracellular replication and growth. It has been shown that the LF can bind to heparan sulfate proteoglycans (HSPGs), which are found on several types of cells. Lang et al. (66) suggest that these cell-surface molecules act as preliminary docking sites for virus spike proteins on the cell surface, thereby playing an important role in severe acute respiratory syndrome coronavirus (SARS-CoV) invasion. Given the similarities observed in both viruses, it is worth pointing out the potentially beneficial role of LF in the ongoing SARS-CoV-2 pandemic (67).

The bacteriostatic properties of LF are mainly based on binding large amounts of iron, and connecting them to bacterial membrane proteins (e.g., LPS). This binding between LF and proteins in bacterial membrane enhances the activity of natural bactericides, such as LZ (see below) (20, 61, 68). Moreover, it was shown that microbial factors can activate Toll-like receptors (TLRs), such as TLR4, in both immune and nonimmune cells of various tissues, including those of the GI tract (69). TLRs are essential for the LPS recognition present in the outer membrane of G(−) bacteria. Studies point out that dendritic cells, differentiated in the presence of LF, displayed reduced reactivity to TLR ligands as well as cytokine secretion, thereby suggesting its anti-inflammatory activity (70, 71). On the other hand, TLR4 responses to LPS affect pathogenic and commensal bacteria, which proves its significant role in balancing intestinal homeostasis, as well as host tolerance (61).

Lysozyme

LZ (muramidase, N-acetylmuramylhydrolase) is an antimicrobial peptide produced mainly by leukocytes and epithelial

cells. LZ represents high enzymatic activity on gram-positive and gram-negative bacteria when administered with LF. The enzyme splits the β-1,4 glycosidic bonds between N-acetylmuramic acid and N-acetylglucosamine in peptidoglycans located in the bacterial wall, thereby causing lysis of microbial factors (72, 73). The concentration of LZ in BC is ~0.3–0.8 mg/L, similar to mature milk (68, 74).

Casein

Caseins are the main proteins of bovine milk (80%) and constitute a minor part of total proteins in human milk (20–50%). These phosphoproteins involve αs1-, αs2-, β- and κ-caseins subtypes, known as casein micelles (75). β-Casein constitutes ~30% of the total protein content in bovine milk (BM) and is represented as A1 or A2 genetic type (76). In many parts of the world, the milk in commercial use contains a mixture of both A1 and A2 caseins (76).

In a mouse model, in which rodents received lethal G(+) and G(−) bacterial injections, researchers observed significantly higher survivability in the group treated with casein (24 h prior to the study) compared with controls (77, 78). Concurrently, A1-caseins were correlated with the induction of inflammation, as well as increased TLR expression in rodent models, compared with A2-caseins and the control group (79). In the following studies, bovine casein salt [sodium caseinate (SC)] intake was shown to correlate with increased proliferation of granulocytic lineage cells in mice. The enhanced granulopoiesis led to increased concentrations of cytokines, such as granulocyte macrophage colony-stimulating factor (GM-CSF) in serum and granulocyte colony-stimulating factor (G-CSF) in serum and bone marrow plasma (80). This increased activation of the innate immune system could elucidate why mice after casein administration were resistant to lethal doses of bacteria presented in previous experiments (77). Recently, the authors of G-CSF pretreatment, which improved survival in the rat sepsis model compared with control, concluded that the pretreatment could be a useful, novel strategy of the treatment in sepsis (81).

Some casein-derived peptides reveal pharmacological similarities to opioids, and can affect GI motility (e.g., β-casomorphins, α-casomorphins, which are fragments of β- and α-casein, respectively) (82). Moreover, it has been confirmed that κ-casein fragments, known as casoxin, act as opioid antagonists (83). Both opioid agonists and antagonists may be formed in the gut in hydrolysis processes of caseins (84). The β- and α-caseins and their derivatives show antioxidant, antimicrobial, and immune-regulating activity (82, 85), while κ-casein fragment (casopiastrin) possesses antithrombotic properties (86). However, in the recent analysis, Fuc et al. (87) revealed that κ-casein proteins also possess immune-modulating activity, and can elicit humoral response similar to α-casein, with variations at the cellular level. Furthermore, κ-casein has been also shown to contribute to cow-milk allergy in the long term.

Glycomacropeptide

GMP, also called caseinomacropeptide, is a milk peptide derived from κ-casein by pepsin or chymosin cleavage (68). GMP binds sialic acid, which, in turn, is responsible for GMP biological activity. Some investigations have shown that GMP possesses prebiotic, antibacterial, and immunomodulatory properties (88): for example, treatment with GMP affects microbiota composition; a significant increase in beneficial microbiota and decrement in pathological bacteria were observed in mouse fecal samples (89).

Proline-rich polypeptide complex

Proline-rich polypeptide complex (PRP), also known as colostrinin (CLN), is a composition of peptides commercially derived from colostrum, mainly composed of proline residues and other hydrophobic amino acids (68). PRP was shown to modulate the immune response (90), and some studies indicate that PRP is a factor influencing both humoral and cellular immunity through the production of cytokines (91). PRP is simultaneously able to stimulate a weakened immune system, and stabilize the immune response when it is hyperactive (e.g., in allergies or autoimmune diseases) (92, 93). Moreover, PRP can reduce the amount of reactive oxygen species (ROS) and inhibit NO (93, 94). Several investigations also described that treatment with PRP improved symptoms in Alzheimer patients with mild-to-moderate dementia (95–98), suggesting its impact on neuronal growth (93–95).

Lactalbumin

LA is composed of whey proteins, including α-lactalbumin (α-LA) and β-lactoglobulin (β-LG). The concentration of α-LA in bovine milk and colostrum is significantly lower than in human colostrum and milk, while β-LG is the most abundant whey protein in bovine milk, and is at the same time absent in human milk. Some benefits of enriching milk in α-LA have been observed primarily in humans and in rodents (95).

Lactoperoxidase

LPO (EC 1.11.1.7) is a glycoprotein that represents oxidoreductase activity found in milk, colostrum, and several exocrine fluids. LPO constitutes ~0.5% of whey proteins in bovine milk, both colostrum and mature milk, and only <0.1% in human milk (68). LPO possesses robust antibacterial and antifungal activity and shows antiviral properties (96). The mechanism of its action is linked to oxidation of thiocyanate (SCN^-), bromide, and iodide ions in the presence of hydrogen peroxide to hypothiocyanous acid (HOSCN), hypothiocyanite ions (OSCN−), and halide ions. These ions can oxidize thiol groups of amino acids in microbial proteins, thereby impairing life functions or cell division of pathogens (68, 97).

Lipids

Lipids present in colostrum contain a wide variety of fatty acids mainly enclosed in the form of mono-, di-, and tri-acylglycerols. It was shown that, during time of

TABLE 2 Vitamin concentrations in bovine colostrum

	Concentration	Reference
Water-soluble vitamins, μg/100 mL		
Thiamin	58–90	(22–24)
Riboflavin	455–483	(23,24)
Niacin	34–97	(22, 23)
Pantothenic acid	173.3	(23,24)
Pyridoxal	15	(23)
Pyridoxamine	21	(23)
Pyridoxine	4	(23)
Biotin	1.0–2.7	(23)
Folic acid	0.8	(27)
Cobalamin	4.9–60	(23, 27)
Ascorbic acid	2.5	(22)
Fat-soluble vitamins		
Retinol, μg/100 g	490	(23)
β-Carotene, μg/100 g	70	(23)
Tocopherol, μg/100 g	290	(23)
Cholecalciferol, μg/100 g	3.05	(23)
Phylloquinone, μg/100 mL	0.49	(23)

lactation, SFAs and PUFAs reduced their content, while the concentration of MUFAs increased as lactation progressed (98).

BC also consists of free fatty acids, glycolipids, phospholipids, steroids, and other agents, like waxes, lipoproteins, or alcanols (51, 99). Choline, another minor component, is present in BC in both the aqueous (free choline, phospho-, glycerophospho-choline) and lipid fractions (phosphatidylcholine and sphingomyelin) (Table 1).

Other components

Colostrum contains several other bioactive components that influence the inflammatory process as well as maintain intestinal immune balance, such as vitamins (**Table 2**), macro- and microelements (**Table 3**), hormones, nucleotides, and gangliosides.

Vitamins are essential in maintaining health. They are also capable of counteracting ROS and inhibiting inflammation. It is worth noting that colostrum alone may contain ROS, which may originate from macromolecules susceptible to peroxidation, or ROS-generating systems for inactivation of infectious factors (99).

TABLE 3 Mineral concentrations in bovine colostrum

Component	Concentration, mg/100 g	Reference
Calcium	472	(22, 23)
Phosphorus	445	(22, 23)
Magnesium	73	(22, 23)
Sodium	106	(22, 23)
Potassium	285	(22, 23)
Zinc	3.8	(23)
Iron	0.2–0.5	(27)
Copper	0.03–0.06	(23)
Sulfur	260	(23)
Manganese	0.01	(23)

The concentration of vitamins in BC depends on a wide range of factors; however, it is worth noting that fat-soluble vitamins (vitamins A, D, E, and K), compared with water-soluble vitamins, do not decrease when colostrum is commercially modified (23).

Finally, sugars such as fructo-, and galacto-oligosaccharides are present in BC. They demonstrate prebiotic properties and promote development of proper intestinal microbiota (*Bifidobacteria* and *Lactobacilli* sp.), thus being responsible for anti-inflammatory properties of BC in the gut (100, 101).

The Role of BC Constituents in IBD

As indicated above, colostrum ingredients represent antimicrobial and immunomodulatory activities that may affect inflammation processes in IBD. Currently, the majority of studies assessing the role of BC constituents and their effects on IBD are based on in vitro studies and rodent models.

Immunoglobulins

No evidence on immunoglobulins from BC was currently found in IBD patients. However, immunoglobulins from serum-derived bovine immunoglobulin/protein isolate in the co-culture model of the intestinal barrier appeared to reduce proinflammatory cytokine production, stabilize the intestinal barrier integrity, and decrease bacterial translocation and thus alleviate antigen-associated inflammation in IBD (34). In humans, the IgA concentration is higher compared with other immunoglobulins, so further investigations should exploit the role of exogenous bovine IgA application in GI diseases (102).

Leukocytes and cytokines

Some research demonstrated that altered secretion of monocytes and macrophages can be observed in IBD; for example, CD patients had increased concentrations of $CD14^+$ and $CD16^+$ monocytes in peripheral blood compared with controls, altered proportions between monocytes to macrophages, and modified immune response of classical monocytes compared with nonclassical or intermediate subsets (103–107).

It should be stressed that CD11b deficiency is correlated with dextran sulfate sodium (DSS)–induced colitis and decreased anti-inflammatory IL-10 secretion (108). In turn, $CD11b^+$ macrophages are predominant CMCs in BC, and they constitute from ~50% to 90% (43, 48). Hu et al. (108) observed that CD11b stimulates IL-10 production and concomitantly attenuates colitis via Src-Akt signaling pathway in mice.

This promotes BC as an attractive anti-IBD agent, as supplementation with IL-10 alone was proved to be insufficient to suppress the entity of proinflammatory mediators in chronic inflammation (109–111). However, it is extremely essential to elucidate whether administration of bovine leukocytes will be able to modify a proinflammatory state through the GI tract in human IBD.

Growth factors

Administration of growth factors contained in BC has been correlated with its beneficial effects on GI diseases in both animal models and humans. Several investigations confirmed the preventive role of IGFs on colonic damage during DSS-induced colitis in mice (112). Moreover, IGFs were shown to play a substantial role in intestinal development (113, 114)—for example, stimulate cell proliferation in small intestinal crypts of piglets (115) as well as diminish bacterial translocation and enhance antiapoptotic activity that protects enterocytes during sepsis (116). The development of inflammation has been associated with reduced IGF-1 synthesis, which may occur in chronic IBD (53). Moreover, correlations between the IGF system alternations and inflammation in IBD patients have been confirmed (113, 114, 117–119). In turn, DeBoer et al. (118) showed that augmented IGF concentrations after anti–TNF-α treatment were associated with increment in both muscle and bone mass in pediatric CD patients.

A study by Oz et al. (120) showed that IL-10 knockout mice fed a TGF-β2–containing diet gained weight and had reduced diarrhea compared with the control group. Other analyses confirmed a relation between TGF-β and Th17 cell differentiation and production of IL-10 as well as maintenance of the intestinal barrier integrity (121). TGF-β induced phosphorylation of protein known as Mothers against decapentaplegic homolog 2 (SMAD2) in LPS- and DSS-induced colitis in mice, and therefore limited endotoxemia, tissue damage, and mortality (122). It is worth mentioning that TGF-β retained its activity upon digestion (123) or pasteurization of bovine milk (124).

Both oral and enteral nutrition with TGF-β significantly mitigated IBD symptoms as well as lessened the severity of disease symptoms (125–127). An example of the above beneficial effects might be clinical remission and diminished inflammation observed (126) in a study in which children received a TGF-β–enriched mixture for 8 wk. In another study, administration of TGF-β2 in the oral polymeric diet, called CT3211, has been correlated with a clinical remission rate in 79% of the pediatric CD patients (128). In a recent study, TGF-β–rich enteral nutritional support appeared to be effective in CD patients as it reduced the severity of IBD symptoms in UC children. The authors suggested that beneficial contribution of TGF-β may become an alternative option of treatment for malnourished pediatric patients (129).

Lactoferrin

Beneficial effects of LF have been studied principally in viral infections including influenza, gastroenteritis, common cold, and herpes (63). Regarding the anti-inflammatory activity of LF (70, 71), it has been shown that altered immune response in IBD may be prevented by modulation of TLR expression (130). These anti-inflammatory effects have been elucidated mainly by in vivo tests and in animal models. In an experimental dextran sulfate–induced mouse model of colitis, oral administration of human LF resulted in diminished inflammation in the LF group compared with control (131). In another study in a DSS-induced mouse model, bovine LF administration did not contribute to apoptotic and necrotic damage but was correlated with limited protection in the intestine by influencing the proinflammatory NF-κB and, potentially, cytokine expression (132).

Beneficial effects of LF supplementation have also been demonstrated in terms of the prevalence of necrotizing enterocolitis in infants with a birth weight $<$1250 g (64). However, in the latest randomized controlled trials (RCTs) it has been proven that enteral supplementation of bovine LF was not correlated with diminished late-onset infection in preterm infants (133). Indisputably, the exact mechanism of LF activity has not been clarified yet, and subsequent studies are highly needed. It should be stressed that administration of LF as a food component is considered safe for humans (63, 68).

Casein

Casein peptides display opioid properties and, in a systematic review, Brooke-Taylor et al. (79) proved that the μ-opioid peptide, β-casomorphin-7 (BCM-7), and other short BCMs (BCM-3, BCM-4, BCM-5) are released through GI digestion from A1 (but not from A2) β-caseins. Some evidence also confirms that BCM-7 is able to display κ-opioid activity and binds to these receptors in the gut (79, 134). Concurrently, some studies demonstrated that BCM-7 shows proinflammatory activity in the GI tract; for example, in a double-blind, randomized crossover study, where adults consumed exclusively either A1 or A2 milk for 2 wk (with a 2-wk washout period after the first stage), significant correlations between subjective markers of discomfort (abdominal pain, bloating) and higher concentrations of fecal calprotectin (a marker of intestinal inflammation) were observed in the first group (135). Moreover, stool consistency, measured by the Bristol Stool Scale, was significantly higher in the A1 milk group, and correlated with softer stools compared with A2. In another double-blind, randomized crossover study, post-dairy digestive discomfort has been observed in people consuming A1 compared with the A2 type of β-casein (136). These, as well as animal studies, also showed that A1 slows GI transit in an opioid-mediated mechanism (137, 138). Despite extensive evidence showing BCM-7 and GI symptom linkages in IBD patients, further extensive clinical studies are highly needed.

Glycomacropeptide

Treatment with GMP has been correlated with changes in the composition of microbiota—that is, a significant increase in beneficial microbiota with a simultaneous decrement in pathological bacteria in mouse fecal samples (89). In line, oral administration of GMP in mice has been associated with augmentation of beneficial *Firmicutes* species (*Allobaculum*) and depletion of *Proteobacteria phylum*, especially *Desulfovibrio* sp., which are linked to IBD pathogenesis (139). Moreover, mice receiving GMP demonstrated significantly higher concentrations of SFCAs, as evidenced in a cecal

analysis. Other investigations in mice confirm that GMP possesses an anti-inflammatory property and can reduce the severity of IBD by concurrent stimulation of the innate immunity and hindering T-cell–driven adaptive immunity (140, 141).

Lactalbumin

The application of α-LA hydrolysates has been correlated with beneficial effects in malnourished children with diarrhea: a greater weight gain and a lower incidence of rehydration were observed; however, no benefits regarding the duration of diarrhea or stool output were found (142, 143). Currently, there are no other investigations showing the effectiveness of α-LA relating to IBD symptoms.

Nevertheless, the digestion of α-LA in the small intestine leads to a release of several peptides with immunomodulatory and antimicrobial activity (95), while other peptides predominantly demonstrate prebiotic activity (144); for example, a tripeptide, Gly-Leu-Phe, has been confirmed to stimulate both murine and human phagocytic cells and to possess a protective role against *Klebsiella pneumoniae* infection (145, 146).

Similarly to casomorphin derivatives, components originated from LA digestion (e.g., β-lactorphin) exhibits opioid-like activity and may influence the endogenous opioid system whose disruptions are observed in and correlated with IBD (147, 148). Moreover, these peptides could potentially modulate immune signaling by changing the gut microbiome.

Lactoperoxidase

LPO has been used to explain inflammation processes in different tissues. Shin et al. (149) observed that virus-infected mice exhibited milder pneumonia symptoms after oral administration of LPO by damping the infiltration of inflammatory cells in the lungs. In a further analysis, the same authors demonstrated that administration of bovine LPO in DSS-induced colitis in mice correlated with decreased IL-6 levels as well as an improved histological score (150).

In other studies, the interplay between LPO and dual oxidase enzyme (DUOX) has been observed in IBD patients. Some studies confirmed that DUOX2/DUOXA2, which forms the predominant hydrogen peroxide–producing system in the human colon, is significantly upregulated in active UC (151). In turn, other authors found a correlation between the DUOX2/DUOXA2 system and inflammation processes in mice (152). Rigoni et al. (153) demonstrated that elevated concentrations of LPO during the healing phase in mouse colitis might support both hydrogen peroxide scavenging and $OSCN^-$ secretion in the epithelium. The authors suggested that different mechanisms for inactivation of microbial factors may have evolved in humans and rodents. Yet, they are all focused on controlling hydrogen peroxide levels and improving mucosal recovery by limiting the extent of hydrogen peroxide scavenging. Even though LPO will probably not be expressed in the human colon (153), BC-derived LPO-scavenging action might play a significant role in the human gut, and further investigations are still required.

Other constituents

In a recent analysis, increased ganglioside catabolism as well as changes in the composition of gangliosides were observed in the intestinal mucosa of IBD patients (154). It was reported that gangliosides containing 3 unsaturated bonds (GD3 and GD1a) were not found in the inflamed intestinal mucosa, unlike the control group. It was suggested that positive effects of a specific dietary ganglioside supplementation include an increase in the intestinal integrity and enhancement of the gut-barrier function. Thus, they may be beneficial in some disorders, such as IBD (155). It is worth noticing that sialoganglioside (GD3) is most abundant in BC (156).

Other studies focused on assessing the role of choline in IBD (157). Lower serum concentrations of choline are common in IBD patients, but no correlation between choline deficiency and the severity of IBD has yet been proved. On the other hand, Sagami et al. (158) suggested that choline deficiency may be beneficial in DSS-induced colitis in mice as it caused a loss of proinflammatory type II NK T cells.

Preclinical and Clinical Studies on BC Supplementation in IBD

Until now, investigations on the anti-inflammatory effect of whole BC had been conducted primarily in vitro and in rodent models and only a few clinical trials in humans had been conducted, and primarily in healthy subjects.

Lee et al. (159) showed that both whole and whey BC fractions can suppress LPS-induced NF-κB activation in mouse adipocytes. Moreover, anti-inflammatory, antioxidative, and antiadipogenic effects of whole BC were significantly higher compared with whey BC. In DSS-induced colitis in mice, administration of BC expedited epithelial regeneration, as well as improved the histologic score of severity of inflammation. Positive results were also linked with reorganization of immunoregulatory mechanisms (17). In the same mouse model, BC supplementation improved occult blood and stool consistency, as well as contributed to clinical recovery from colitis. However, it did not prevent an initial weight loss (160). In a recently published study using the 2,4,6-trinitrobenzenesulfonic acid (TNBS) colitis model it has been observed that BC therapy alleviates intestinal damage and ameliorates clinical symptoms in mice (130). The authors propose that benefits have their origin in the modulation of inflammatory response through TLRs as well as in stabilization of the growth of beneficial bacteria. Current studies evaluating the beneficial influence of BC on humans have been conducted in healthy subjects, mainly athletes and children.

In human peripheral blood mononuclear cells (PBMCs) of 4 male endurance athletes, BC concentrate supplementation was correlated with cytokine secretion (49). It was demonstrated that the concentrate of BC enhanced the secretion of IL-2, IL-10, and IFN-γ, while addition of LPS to PBMCs correlated with a release of IL-2 and inhibited

secretion of TNF, IL-6, and IL-4 in the early phase. Beneficial effects of BC have been reported in a meta-analysis evaluating the effects of BC supplementation during training and related to upper respiratory symptoms. However, it was observed that the majority of clinical trials (4 of 5) were associated with a moderate- or high-risk bias due to poor reporting practices (161).

In a recent study, Hałasa et al. (162) demonstrated that the zonulin concentration as well as the lactulose to mannitol ratio were decreased by supplementation of 500 mg colostrum for 20 d in 16 athletes during peak training before a competition. In another investigation, the effectiveness of BC supplementation was evaluated on exercise-induced intestinal permeability in high temperature during a 14-d period. Supplementation of 20 g/d colostrum reduced intestinal pain compared with the control group, but had no impact on circulating concentration of bacterial DNA (163).

A meta-analysis including 5 RCTs (324 patients) revealed significant benefits of BC therapy in children (164). The BC treatment was effective in the prevention of diarrhea episodes, upper respiratory tract infection, and hospitalization. The authors concluded that BC and related products (hyperimmune BC and immunoglobulins derived from BC) have a considerable impact on children with infectious diarrhea and should be considered during its treatment.

Notwithstanding the aforementioned promising results, currently there are no investigations pertaining to the efficacy of oral BC supplementation in IBD patients. In this regard, further high-quality RCTs are urgently needed. In a study by Bölke et al. (165), oral pretreatment with BC significantly reduced endotoxin concentrations and shortened endotoxemia in patients who underwent an abdominal surgery compared with the control group. A study on the efficacy of BC enemas in the treatment of UC was conducted by Khan et al. (166). In a double-blind randomized trial, patients with left-sided colitis were treated with BC or control solution for 4 wk. All patients also received mesalazine at a dose of 1.6 g/d. If the patients had been undergoing mesalazine treatment upon inclusion in the study, the dose was increased accordingly. In the BC group, a significant alleviation of symptoms compared with controls was reported.

Due to the lack of studies assessing BC impact on humans, an analysis of its potential contraindications seems essential. An additional limitation on the use of BC products described by its manufacturers includes allergy to cow milk. This, however, has not been clinically confirmed.

What is noteworthy is the fact that, in the latest International Olympic Committee (IOC) statement, BC has been classified as a supplement, which may indirectly improve performance. Other nutritional supplements included into this group were polyphenols, glutamine, caffeine, or omega-3 PUFAs (167).

Conclusions

BC includes a gamut of bioactive constituents, which together may alleviate the clinical course of inflammatory diseases, such as IBD. Currently available therapeutic approaches for IBD patients are still insufficient and future treatment options with novel mechanisms are urgently needed. Due to the lack of studies on the impact of BC on humans, an analysis of not only several benefits but also potential contraindications of its usage is essential. BC has been shown as an efficient anti-inflammatory supplement as a whole. Also, its constituents alone are taken into consideration. Studies suggest that BC may counteract primarily the increase in proinflammatory cytokines, but the observed complexity of a cytokine storm in IBD patients allows to conclude that beneficial effects of BC also stem from other mechanisms of action. Therefore, it is essential to further elucidate the beneficial effects of BC in IBD—for example, by determining whether modulation of either monocyte or macrophage representation with the use of colostrum will be able to diminish the pro-inflammatory state through the GI tract in human IBD. Moreover, future studies should clarify the influence of orally consumed colostrum on the human body due to a potential change in the biological activity of its constituents during digestion, as well as a change in pH depending on the GI tract segment. Another relevant issue pertains to understanding the interplay between the BC constituents such as GMP, PRP, or LA with the microbiota and immunity. On the other hand, some BC components, such as LA, may become valuable food components in the future. However, in order to support this assumption, further research is also needed. Undeniably, preserving the high quality of commercially available colostrum to maintain its beneficial activity far beyond harvest and processing is also highly important.

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