NFS Journal 25 (2021) 1–11

Contents lists available at ScienceDirect

NFS Journal

journal homepage: www.elsevier.com/locate/nfs

Review article

Bovine colostrum: A source of bioactive compounds for prevention and treatment of gastrointestinal disorders

Rhaabe D.S. Gomes [a], Katya Anaya [b,*], Alyne B.S. Galdino [a], Juliana P.F. Oliveira [c], Marco A. S. Gama [d], Caroline A.C.X. Medeiros [e], Elaine C. Gavioli [f], Ana Lúcia F. Porto [g], Adriano H. N. Rangel [a]

[a] Postgraduate Program in Animal Production, Universidade Federal do Rio Grande do Norte – UFRN, Macaíba, RN, Brazil
[b] Faculty of Health Sciences of Trairi, Federal University of Rio Grande do Norte – UFRN, 59200-000 Santa Cruz, RN, Brazil
[c] Rural Health and Technology Center, Federal University of Campina Grande -UFCG, 58428-830 Patos, PB, Brazil
[d] Embrapa Gado de Leite, Avenida Eugênio do Nascimento, 610 Juiz de Fora, MG, Brazil
[e] Postgraduate Program in Biotechnology RENORBIO/ Postgraduate Program in Biological Sciences/ Department of Biophysics and Pharmacology, Federal University of Rio Grande do Norte – UFRN, Natal, RN, Brazil
[f] Department of Biophysics and Pharmacology, Federal University of Rio Grande do Norte – UFRN, Natal, RN, Brazil
[g] Departamento de Morfologia e Fisiologia Animal, Universidade Federal Rural de Pernambuco, 52171900 Recife, PE, Brazil

ARTICLE INFO

Keywords:
Functional food
Intestinal permeability
Gastrointestinal infection
Inflammatory bowel disease
Immunomodulatory effect
Oral supplementation

ABSTRACT

Bovine colostrum is a rich source of nutrients and biologically active molecules known to be able to modulate the human immune system, such as lactoferrin, lysozyme, lactoperoxidase, immunoglobulins and growth factors. This comprehensive review aimed to gather evidence from animal experimentation and clinical trials that investigated the potential effects of bovine colostrum in preventing and treating diseases that affect the human gastrointestinal tract. Considered safe for human consumption, BC or its isolate components were used against a range of different gastrointestinal disorders. Beneficial effects were observed in several conditions: gastrointestinal infections, infectious diarrhoea, drug-induced lesions, gut-barrier malfunction, and inflammatory bowel disease. Under proper processing to maintain its components' integrity, BC products are valuable supplements with high nutraceutical value, capable of promoting and restoring gastrointestinal health.

1. Introduction

Bovine colostrum (BC) is the first milk secretion of the mammary gland of cows after calving. It is rich in immunoglobulins, lactoferrin, lysozyme, lactoperoxidase, growth factors and bioactive peptides. Colostrum has higher levels of protein, fat, vitamins, and minerals when compared to milk. This compositional singularity of colostrum enables full development of the newborn calf, in addition to guaranteeing immunity against several pathogens [1–4].

A healthy cow produces approximately 5 to 10 L of colostrum per milking [5], an amount that usually exceeds the requirements of the newborn calf. Therefore, its surplus can be used in producing food, supplements, or medicines. However, special care must be given to its storage and processing so as not to compromise the biological activity of its components and consequently its therapeutic effect [6]. The dairy industries do not commercially exploit colostrum on a large scale due to processing and storage problems, such as its low coagulation temperature, which affects pasteurization [1,7]. Apparently, most BC metabolites' concentration is preserved or mildly affected if a gentle heat treatment procedure is applied (60 °C, 25–30 min pasteurization) [8,9]. Even though heat treatment can compromise bioactive proteins due to denaturation, their abundance in BC is sufficient to exert beneficial effects [7,10]. Most of the commercially available BC products on the market are prepared by freeze-drying or spray drying, aiming to maintain the biological activity of its components [11–15]. These products are often ready for consumption and made up of mixtures with skimmed-milk powder, whey powder, and whole milk [1,4].

BC is reported as safe for human consumption. There are no

* Corresponding author at: Faculdade de Ciências da Saúde do Trairi – FACISA, Universidade Federal do Rio Grande do Norte, 59200-000 Santa Cruz, RN, Brazil.
E-mail addresses: rhaabe.dayane@hotmail.com (R.D.S. Gomes), katya.anaya@ufrn.br (K. Anaya), alynebs@outlook.com (A.B.S. Galdino), jupaula.oliv@yahoo.com.br (J.P.F. Oliveira), marco.gama@embrapa.br (M.A.S. Gama), carolaufrn@gmail.com (C.A.C.X. Medeiros), egavioli@hotmail.com (E.C. Gavioli), ana.porto@ufrpe.br (A.L.F. Porto), adrianohrangel@yahoo.com.br (A.H.N. Rangel).

https://doi.org/10.1016/j.nfs.2021.10.001
Received 6 July 2021; Received in revised form 3 October 2021; Accepted 4 October 2021
Available online 7 October 2021

contraindications regarding high dose intake and few side effects of clinical relevance have been registered [16,17]. Due to its composition, BC consumption is being encouraged as a nutritional supplement for newborns, children, and adults who have no restrictions on bovine milk consumption [18]. An increasing number of clinical trials gather significant results that advocate in favour of the use of bovine colostrum as a nutraceutical food or supplement (*e.g.* https://trialbulletin.com/lib/trials/term=Colostrum). Its beneficial effects on prophylaxis and treatment of gastrointestinal disorders (Fig. 1) are mainly related to the numerous immunomodulating components, which maintain and recover gastrointestinal tract health [19]. Several studies indicate that colostrum consumption can reduce the occurrence and severity of digestive disorders such as diarrhoea and alleviate inflammatory bowel disease. It can also contribute to preventing and treating colon problems, short bowel syndrome and constipation [4,16,20–22]. Furthermore, there is evidence showing the relationship between the immune responses triggered in the intestine by BC supplementation and the immunity of the respiratory system [23].

This review presents the main scientific evidence on the effects of bovine colostrum supplementation on preventing and treating human gastrointestinal tract diseases and symptoms.

2. Chemical composition of bovine colostrum

As the first milk secreted by female mammals to nourish their offspring after delivery, colostrum is responsible not only for supplying nutrients, but also antibacterial substances and growth factors [2]. It provides the newborn with immunological protection against pathogens and plays an essential role in their physiology, directly influencing their growth and development. Colostrum composition differs from that of mature milk especially due to the presence of immunological and biologically active components (including immunoglobulins, leukocytes, lactoferrin, lysozyme, cytokines, growth factors, hormones, and oligosaccharides), thereby making it a product of great interest for utilization by the pharmaceutical and food industries [1,4].

The rich composition of BC propels its use in human nutrition as a source of bioactive components potentially capable of promoting health improvements by preventing and treating several diseases (Fig. 2) [23–25]. It has already been used in desserts, beverages, and as a food supplement in some countries [20]. It is available on the market as tablets, powder, concentrate, capsules, chewing gum, milk supplemented with colostrum, ice cream, curd, yoghurt, and milk beverages with colostrum added, among other products [26–29]. It is worthy of mentioning that there is great variability in the bioactivity of worldwide commercially available BC products [15].

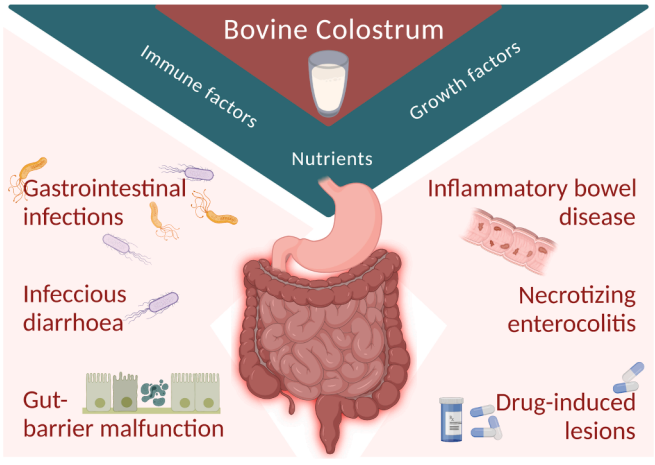

Fig. 1. Bovine colostrum components, especially immune and growth factors, are related to positive effects on the gastrointestinal tract in different impaired conditions. Created with BioRender.com.

BC chemical constituents can be divided into three main categories: nutritional components, immune factors, and growth factors. Nutritional components include the well-known macro and micronutrients present in milk (proteins, lipids, sugars, vitamins, and minerals). Immunoglobulins (IgA, IgG, and IgM), lactoferrin, lysozyme and lactoperoxidase are the immune factors. Within the growth factors, there are epidermal growth factor (EGF), fibroblast growth factors (FGF1 and FGF2), insulin-like growth factors (IGF-I and IGF-II), transforming growth factors beta (TGF-b1 and TGF-b2), platelet-derived growth factor (PDGF) and betacellulin (BTC) [12,30]. Table 1 shows the nutrients and bioactive compounds present in bovine colostrum.

The nutritional composition of colostrum varies according to the breed, calving order, feeding and health status of the cow. Furthermore, the postpartum time also directly influences its composition, especially when we compare the colostrum collected in the first postpartum hours with that obtained in subsequent milkings (usually referred to as transition milk), as well as with mature milk (Table 2) [31,33,34].

2.1. Bovine colostrum immune factors

2.1.1. Immunoglobulins

Immunoglobulins G (IgG), A (IgA) and M (IgM) are present in bovine colostrum. They are found in high concentrations in colostrum, which contributes to its high protein content in BC. IgG corresponds to about 80% of the total amount of immunoglobulins [16,35,36]. The primary function of immunoglobulins is to provide passive immunity to the calf once, except for IgG, maternal immunoglobulins in cattle cannot cross the placental barrier to the fetus [37].

Immunoglobulins are well known for their benefits to human health in terms of the immunogenic response. When hosts are exposed to foreign bodies (antigens), these antibodies bind, recognise, and destroy bacteria, toxins, viruses, and other antigens. The immunoglobulins levels in bovine colostrum are about 100 times higher than those found in mature milk [38,39].

2.1.2. Lactoferrin

Lactoferrin is an iron-binding glycoprotein present in body secretions such as tears, sweat, semen, saliva, and colostrum. Like the other immune components of BC, its concentration decreases over the hours after delivery and is present in a lower concentration in mature milk. The lactoferrin concentration in BC and mature milk generally varies between 1.5 and 5 mg/mL and 0.02–0.75 mg/mL, respectively [31].

Lactoferrin displays important activities, such as antioxidant, antimicrobial and immunomodulatory. Moreover, it increases the proliferation and differentiation of intestinal epithelial cells. Thus, lactoferrin constitutes a vital role in the innate immune system [40,41]. Research has shown that lactoferrin has a high resistance rate to digestion, and promotes benefits to children's intestinal health by reducing the pathogenic microbial load [42]. The biological activities of lactoferrin are related to its basic N-terminal domain, which interacts with various microbial and host targets [43].

2.1.3. Lysozyme

Lysozyme is an antimicrobial enzyme present in milk, colostrum, and other bodily secretions. It hydrolyses the peptidoglycan layer of the bacterial cell wall, causing the lysis of gram-positive and gram-negative bacterial cells. Lysozyme concentration is higher in colostrum than in milk, varying between 0.14 and 0.7 mg/L and 0.07–0.6 mg/L, respectively [4,16,31].

2.1.4. Lactoperoxidase

Lactoperoxidase (LP) is an enzyme belonging to the peroxidase family, which occurs naturally in colostrum and other body secretions. Its function is to catalyse the oxidation of thiocyanates. Lactoperoxidase catalyses an antimicrobial system from thiocyanate ion (SCN-) and

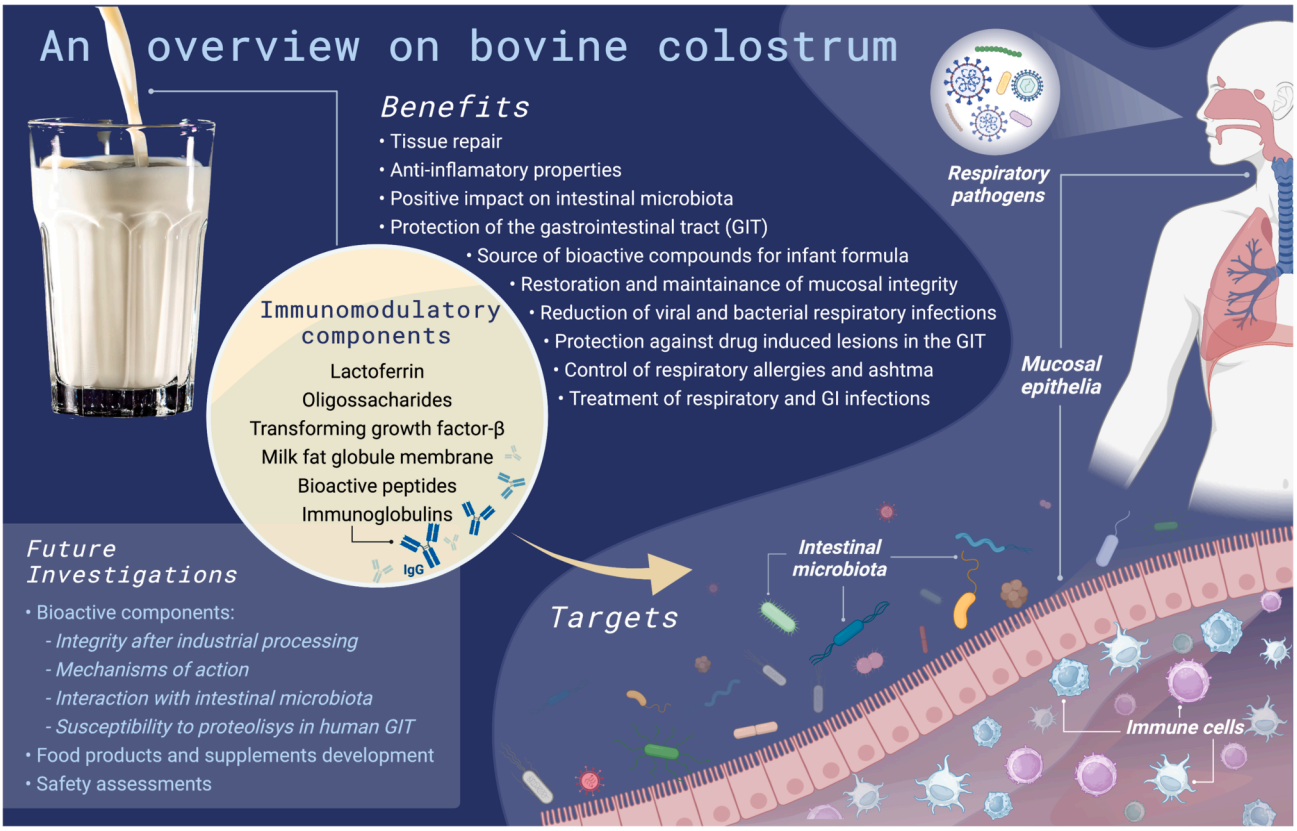

Fig. 2. Benefits associated with the intake of bovine colostrum or its isolated immunomodulatory components. GI: gastrointestinal; GIT: gastrointestinal tract. Based on data synthesized by Galdino et al. [23], Sangild et al. [24], and Arslan et al. [25]. Created with BioRender.com.

Table 1
Bovine colostrum chemical composition.

Carbohydrates	Lactose and oligosaccharides
Proteins	Casein, Immunoglobulins (IgG, IgA, and IgM), Lactoferrin
Lipids	Short, medium and long-chain fatty acids, mostly saturated
Minerals	Ca > K > Na > Mg, Zn > Fe
Vitamins	A, E, D, K, C and B complex
Free amino acids	Lys > Phe > His > Leu > Glu > Ile > Val > Met > Pro
Cytokines	Interleukins, Tumour necrosis factor, Interferon
Growth Factors	Epidermal growth factor (EGF), Betacellulin (BTC), Insulin-like growth factor (IGF-1), Transforming growth factor β1 (TGF-β1), fibroblast growth factor 1 and 2 (FGF1 and FGF2), platelet-derived growth factor (PDGF)
Enzymes	Lactoperoxidase, Lysozyme, Proteinases, Lipases, Esterases

Adapted from Buttar et al. [18], McGrath et al. [31] and Bartkiene et al. [32].

Table 2
Compositional differences between bovine colostrum and mature milk.

Constituents (%)	Colostrum*	Mature milk
Lactose	2.7	5.0
Fat	6.7	4.0
Protein	14.0	3.1
Casein	4.8	2.5
Ash	1.11	0.74
Total solids	23.9	12.9
Solids-not-fat	16.7	8.8

Adapted from Borad & Singh [12].
* First postpartum milking.

hydrogen peroxide, generating oxidation products that inhibit bacteria, protozoa, and fungi growth. The LP concentration in the colostrum is low and increases over the postpartum days, being the enzyme with the highest concentration in milk. Usually, LP participates in the body's natural defence system [12,16,44].

2.2. Bovine colostrum growth factors

Bovine colostrum contains about 50 polypeptides described as growth factors. The main growth factors include epidermal growth factor (EGF), betacellulin (BTC), insulin-like growth factor (IGF-1), transforming growth factor β1 (TGF-β1), fibroblast growth factor 1 and 2 (FGF1 and FGF2) and platelet-derived growth factor (PDGF) [31]. These polypeptides have multiple functions in the body but are found in low concentrations in mature milk, which reinforces the importance of evaluating the therapeutic benefits of colostrum. Once most of the growth factors present in bovine colostrum appear to resist thermal treatments up to 60 °C [15], new techniques have been developed for their extraction in bovine colostrum and whey [45]. Polypeptides such as EGF, IGF-1 and TGF-β1 can be absorbed intact in the gastrointestinal tract or partially degraded [35,44,45].

BC also contains bioactive peptides, which are encrypted within the sequence of their original protein molecule. They can be released as a result of lactic acid bacteria and probiotic strains activity, which are highly proteolytic and fragment proteins. This release of bioactive peptides from colostrum proteins can occur faster during the colostrum fermentation process [46,47]. The function of bioactive peptides varies according to the length and sequence of amino acids. Some of the bioactive peptides found in milk and colostrum have been shown to display antihypertensive, antioxidant, antithrombotic, antimicrobial, and immunomodulatory functions [44].

3. Effects of colostrum on gastrointestinal tract disorders

Supplementing the human diet with BC modulates immune system

responses, improving symptoms of diseases that affect the gastrointestinal tract (GIT). Recent research has demonstrated beneficial effects of BC components against various gastrointestinal disorders, especially on inflammation, treating or preventing secondary ulceration and diarrhoea caused by viruses [16,48–50]. Apparently, the anti-inflammatory activity of BC in intestinal epithelial cells is related to the suppression of nuclear factor-κB expression [51]. GIT health benefits related to whole BC or isolate components supplementation are summarised in Table 3.

BC can also be used as adjunctive therapy to alleviate side effects caused by drugs, where the gastrointestinal tract suffers injuries and is weakened due to pharmacological therapies. BC was able to reduce inflammation of oral and intestinal mucosa caused by cancer treatments [4,16,18].

Another promising application of BC supplementation is in children with autism spectrum disorders (ASD). They are prone to gastrointestinal disorders such as diarrhoea, irritable bowel syndrome and bacterial dysbiosis. Sanctuary et al. studied the effects of BC and BC combined with a probiotic strain supplementation in a pilot study with children with ASD [52]. In this 10-week double-blind, crossover, randomised intervention, there was an improvement in chronic gastrointestinal symptoms such as pain with stooling, frequency of diarrhoea and stool consistency. However, larger trials, preferably placebo-controlled, are needed to determine the efficacy of these treatments.

3.1. Gastrointestinal infections

Yadav and co-workers tested BC antimicrobial and anti-inflammatory activity in rats underwent induced edema [86]. Colostrum reduced the growth of five bacteria strains (*Escherichia coli, Staphylococcus aureus, Proteus vulgaris, Enterobacter aerogenes and Salmonella typhi*) and edema. In another study, bovine colostrum proved to be effective in reducing enterotoxigenic *E. coli* colonization and was also able to modulate the intestinal immune system of piglets when compared to a group fed with a milk replacer [54]. BC can also be used to reduce uropathogenesis caused by the gastrointestinal carriage of *E. coli*, as demonstrated by Larcombe et al. [53]. These authors used hyperimmune colostrum as a therapy against *E. coli* in mice, resulting in interruption of gastrointestinal colonization. The product called "hyperimmune colostrum" is obtained through cows' immunization with the microbial strains of interest, resulting in colostrum with specific antibodies [87]. A *Clostridium difficile* toxin–specific hyperimmune bovine colostrum was effective against *C. difficile* infection (CDI) in piglets. Liquid and freeze-dried hyperimmune colostrum are suggested to be used as immunoglobulin-driven treatments to control CDI, as safe, affordable and specific antibiotic alternatives which spare the colonic microbiota [55].

Promising products are being developed and can potentially be used as functional foods, helping to prevent gastrointestinal infections [88]. Bartkiene and co-workers evaluated the influence of fermentation with *Lactobacillues plantarum* and *Lactobacillus paracasei* and different drying methods in the amount of IgG, IgA, and IgM in bovine colostrum and antimicrobial activity in BC products. The fermented colostrum products inhibited the growth of 12 pathogens and showed high IgG and IgM content [89].

In sepsis cases, the intestinal release of endotoxins by pathogens plays an important role in infectious complications [90]. The oral consumption of colostrum is suggested as a prophylactic strategy for surgical patients because it reduces the translocation of gut-derived Gram-negative bacterial lipopolysaccharide (LPS, or endotoxin), inhibiting enterogenic endotoxemia [91]. In animal experiments, BC and BC enriched with lactoferrin had proven to reduce 67% and 80% of the plasma levels of endotoxins, respectively [56].

A BC commercially available concentrate supplement was successfully used in a randomised pilot human study to reduce endotoxin levels generated after abdominal surgery, as demonstrated by Bölke et al. [57]. In the mentioned study, patients orally received a preparation containing colostrum immunoglobulin before surgery to assess the action on intra- and post-operative plasma endotoxin levels. The group which received the oral BC preparation had significantly lower levels of endotoxin and endotoxin-neutralizing capacity.

3.1.1. Helicobacter pylori infection

H. pylori is considered one of the most common bacterial infections in humans. The infection is caused by oral ingestion of the bacterium, transmitted in early childhood; however, its elimination in children can be spontaneous [92]. *H. pylori* infection is highly associated with several gastrointestinal disorders, including chronic gastritis, peptic and duodenal ulcers, and gastric adenocarcinoma [93]. A consensus report published in 2017 recommends treating *H. pylori* gastritis for all infected subjects [94]. The prevalence *H. pylori* infections are higher in developing countries and poor socioeconomic conditions [95].

Decades ago, an *in vitro* study showed the ability of colostrum to inhibit the binding of *H. pylori* and *Helicobacter mustelae* to lipid receptors [96]. BC concentrate partially inhibited microbial adhesion to specific lipids (putative receptors for microbe-host cell membrane interaction), demonstrating that colostrum lipids can modulate the interaction of *H. pylori* and other pathogens with envelope adhesins.

In mouse models, hyperimmune bovine colostrum has successfully reduced *Helicobacter* spp. infections [59]. Mice infected with *H. felis* received hyperimmune colostrum associated with antibiotics after infection. Bacterial load reduction was significant when colostrum was co-administered with amoxicillin [97]. Tran et al. evaluated four therapies combining hyperimmune colostrum, amoxicillin, zinc and acetylcysteine. The therapies combined with hyperimmune colostrum were effective in reducing the *H. pylori* bacterial load [58].

Isolate bovine lactoferrin was tested in a clinical trial [60]. The volunteers (50 patients infected with *H. pylori*) were divided into two groups: one group received traditional therapy (clarithromycin, omeprazole, amoxicillin, or metronidazole), and the other group received conventional therapy plus lactoferrin. The addition of lactoferrin to conventional treatment improved the *H. pylori* eradication rate compared to the control group (92% *versus* 68%), showing that lactoferrin can effectively treat infection by this bacterium.

The studies presented herein have shown that BC and lactoferrin, one of its bioactive components, are effective in fighting infection by bacteria of the *Helicobacter* spp. genus. The mechanisms of action of BC components against *Helicobacter* spp. growth require further investigation.

3.2. Infectious diarrhoea

Diarrhoea is a digestive disorder that can be caused by several pathogens, especially *E. coli*, rotavirus and *Cryptosporidium* spp. Supplementation with BC has shown action against these pathogens [30], and rich evidence has been gathered over the years, confirming its benefits.

The effect of colostrum consumption has been studied in animals infected with human pathogens, demonstrating beneficial effects against agents which cause diarrhoea. Inagaki et al. developed a study to determine the effect of colostrum administration on human rotavirus infection in lactating mice [66]. To this end, different doses of skimmed and concentrated bovine colostrum were administered, resulting in relief of diarrhoeal symptoms. The authors recommend the use of BC for protection against severe rotavirus-induced gastroenteritis for immunocompromised hosts, such as children and older adults.

Kaducu and co-workers conducted a study to investigate the effects of colostrum supplementation on treating HIV-associated diarrhoea [65]. A total of 45 patients received 50 g of the commercially available colostrum-based food product twice daily for 28 days. There was a significant decrease of 79% in the evacuation frequency in patients on the colostrum-based supplement at the 4th week compared to the placebo group (58% decrease). The reduction in the evacuation frequency was

Table 3
Effects of bovine colostrum or bovine colostrum isolate compounds supplementation on the gastrointestinal tract health observed in animal experimentation and human studies.

Application		Studied sample	Intervention	Main benefits	Reference
Gastrointestinal infections		40 piglets	Liquid BC prepared by mixing BC powder with water (approximately 150 g of powder in 1 L of water), *ad libitum* for 8 days	Reduction of enterotoxigenic *Escherichia coli* Modulation of the intestinal mucosal immune system	[53]
		40 weak piglets	Commercial skimmed standardised BC product, *ad libitum* for 8 days	Reduction of the frequency of diarrhoea in piglets with incompetent intestinal immune system by modulation of the immune response Lowering colonization of enterotoxigenic *E. coli* (ETEC F18) in the intestinal tissue	[54]
		23 piglets	25 mL Hyperimmune bovine colostrum (HBC), twice daily for 7 days, oral administration after inoculation	Reduction or absence of diarrhoea in *C. difficile* infected animals Preservation of normal human gut microbiota	[55]
		35 male Wistar rats	400 mg iron saturated BC/kg of different compositions; 400 mg type 2 BC/kg plus 80 mg bovine iron saturated lactoferrin/kg	Reduction of both endotoxin activity in plasma and bacterial contamination of the peritoneal cavity in experimental septic shock	[56]
		40 patients (22 male, 18 female)	56 g of colostral preparation (Lactobin™), for 3 days, pre-operatively. Daily dose divided into four parts (before breakfast, at lunch, at supper, and at night rest)	Reduction of circulating endotoxin levels and inhibition of the decrease of plasma endotoxin-neutralizing capacity during abdominal surgery	[57]
	Helicobacter pylori infection	54 C57BL/6 female mice	0.1 mL HBC + *N*-acetylcysteine + zinc + amoxicillin A, twice a day, for 10 days, by oral gavage	Eradication of *H. pylori* infection	[58]
		100 mice	Bovine colostral hyperimmune immunoglobulin preparation or immunoglobulins from non-immunized animals in concentrations of 0.1, 10 or 50 mg/mL in the drinking water (around 20 mg/mL), for 10 or 20 days.	Infection cure rate of 66% Reduction of colonies number	[59]
		50 patients, both gender	Traditional therapy (clarithromycin, omeprazole, amoxicillin, or metronidazole) *versus* traditional therapy plus lactoferrin (Pravotin™), for 1 week. Orally taken 2 h after break-fast (200 mg) and 2 h after dinner (100 mg)	Improvement of the eradication rate *of H. pylori*	[60]
Gut-barrier malfunction		14 patients (6 male, 8 female)	100 mL of 10% colostrum solution, orally, twice a day, for 4 weeks	Decrease of intestinal permeability Prevention of gastric lesions induced by non-steroidal anti-inflammatory drugs	[61]
		70 patients (35 male, 35 female)	BC powder 20 g/ day, three times per day, for 10 days, enteral nutrition, in ICU patients	Decrease of intestinal permeability Reduction of the incidence of diarrhoea	[62]
		16 healthy male athletes	500 mg of BC powder, orally, twice daily, for 20 days	Decrease of intestinal permeability	[63]
		12 healthy male athletes	High-protein BC powder (NZMP™), 20 g/d, orally, for 14 days +14-d washout	Reduction of the exercise-induced increase in gut permeability	[64]
Infectious diarrhoea	Human rotavirus infection	BALB/c mice, 5-d-old	Skimmed and concentrated bovine late colostrum dissolved in 50 μL of PBS, given orally by gavage, 60 min before viral inoculation	A dosage greater than 1.0 mg, 60 min before viral inoculation, prevented the development of diarrhoea Relief of HRV-induced diarrhoeal symptoms	[65]
	HIV-associated diarrhoea	87 men	50 g of colostrum-based supplement (powder, orally, twice a day for 28 days)	Decrease of evacuation frequency Promotion of weight gain	[66]
	Rotavirus and *E. coli* infection-related acute diarrhoea	160 children, aged 6 m to 2 y	3 g BC powder diluted in 50 mL water, daily, orally, 1 week	Reduction of frequency and duration of vomit and diarrhoea episodes	[22]
	Enterotoxigenic *E. coli* (ETEC) infection	90 healthy volunteers	One or two tablets with 200 mg of HBC powder, three times a day for 7 days	Protection against the development of diarrhoea Reduction of abdominal pain complaints No effect on the viability of the challenge strains	[67]
Necrotizing enterocolitis		40 preterm piglets	2 days of total parenteral nutrition, followed by a rapid transition to full enteral feeding (15 mL/kg) for 2 days using BC	Lower incidence and severity of NEC in comparison to infant formula-fed piglets	[68]
		34 preterm pigs	Total enteral nutrition groups fed either milk formula, 6 h of milk formula followed by BC, or only BC, 15 mL/kg body weight/ 3 h.	Increase of villi height, galactose absorption and brush-border enzyme activities in the distal small intestine	[69]
		61 preterm pigs	BC + donor human milk, 24 to 40 mL/kg/d on days 1–2 to 120 mL/kg/d on days 3–5, enteral nutrition supplemented with parenteral nutrition	Superior benefits of BC on the improvement of gut function, nutrient absorption, and bacterial defence mechanisms in comparison to formula-based fortifiers	[70]
		80 preterm neonates	BC administered as gut priming	Decrease of feeding intolerance, NEC, late-onset sepsis and mortality	[71]
Drug-induced lesions		36 rats (gastric-induced damage)	Rat model: 2 mL BC, 25% and 50% vol/vol, oral administration. Indomethacin damage (20 mg/kg, subcutaneously) was induced 30 min after gavage	Gastrointestinal restoration. Pre-treatment with 0.5 or 1 mL colostral preparation reduced gastric injury by 30% and 60%, respectively, in rats	[72]
		100 mice (small intestinal induced injury)	Mouse model: drinking water supplemented with 5% and 10% solution of BC for six days (approximately 5 mL/mouse/day). Indomethacin (85 mg/kg, subcutaneously) was administered 24 h before the end of the study	Prevented villus shortening in the mouse model of small intestinal injury	

(*continued on next page*)

Table 3 (*continued*)

Application	Studied sample	Intervention	Main benefits	Reference
	48 male mice	Diclofenac +5% BC for 7 days, in drinking water	Reduction of the increase in intestinal permeability induced by diclofenac, reduction of gut barrier dysfunction and intestinal villous damage Reduction of bacterial overgrowth	[73]
	45 female mice	Hydrolysed lactoferrin isolated from bovine colostrum (C-lobe) (200 mg/kg weight), orally given to mice submitted to NSAIDs (10 mg/kg) gastrointestinal damage	Sequestration of unbound NSAIDs molecules in the gut, resulting in the reversal of NSAID-induced gastropathy	[74]
	24 male rats	BC commercial products, 2 mL (7 mg/mL), oral administration. Indomethacin damage (20 mg/kg, subcutaneously) was induced 30 min after gavage	Restoration of gastric mucosa	[15]
	37 pigs	BC, busulfan plus cyclophosphamide, 11 times/ d (15 mL/kg), orally	Reduction of gut toxicity during myeloablative chemotherapy Enhancement of intestinal enzyme activity	[75]
	21 weaned pigs	Mucositis induction with doxorubicin at 3.75 mg/kg. BC (5 mL/kg), 3 times daily, beginning the day before and continuing after lesion induction	Reduction of mucositis severity in the small intestine	[76]
	7 healthy male volunteers	Liquid BC, 125 mL three times daily, before and after 5 days of 50 mg of indomethacin	No significant increase in permeability was seen when colostrum was co-administered	[77]
	62 children 1–18 years old	Spray-dried BC powder (Biofiber-Damino™), 7.5–30 g/ day (according to the bodyweight), 1–3 daily doses, oral or nasogastric tube	No difference for neutropenic fever, intravenous antibiotics, incidence of bacteremia, or intestinal mucositis Reduction of the peak severity of oral mucositis	[78]
Inflammatory bowel disease (Ulcerative colitis and Crohn's disease)	Female mice	BC powder (Bioversan™) (20 or 200 mg/kg/d), bovine Ig-enriched colostrum powder (Immunolac™) (20 mg/kg/d) dissolved in water. Oral gavage for 14 d before induction of colitis.	Acceleration of epithelial regeneration Induction of immunoregulatory mechanisms Colitis with lower clinical severity and less weight loss	[79]
	NMRI female mice	Pure BC, BC (20 mg/kg) or colostral bovine lactoferrin (bLf, 150 mg/kg), 100 μL, daily, oral gavage, either two weeks before induction of colitis (prophylaxis) or after disease establishment (therapy)	Whole BC prevented injury and improved the recovery from dextran sulfate sodium (DSS)-induced colitis	[80]
	24 CD-1 mice	BC powder (100 mg dissolved in 0.6 mL of saline solution), gastric gavage, for 7 days	Reduction of body weight losses after TNBS-induced colitis Reduction of inflammatory markers and intestinal microbiota	[81]
	24 CD-1 male mice	BC powder (100 mg dissolved in 0.6 mL of saline solution), daily, by gavage, for 21 days	Pre-treatment with BC promoted reduction of intestinal damages and clinical signs of the colitis Downregulation of toll-like receptor 4 (TLR4) and cytokine expression Stabilisation of intestinal microbiota, favouring the growth of beneficial bacteria	[82]
	Female C57Bl/6 J mice	Preventive treatment: 100-500 mg/kg/day IMM-124E (colostrum-based product from cows immunized with LPS from *E. coli*), oral gavage, starting two days before colitis induction. Therapeutic treatment: 500 mg/kg/day IMM-124E, starting at day three of colitis induction. Transfer model colitis treatments: 25 mg/kg, 100 mg/kg, or 500 mg/kg IMM-124E once per day.	The hyperimmune colostrum-based product was effective in ameliorating colitis in the two different mouse models of intestinal inflammation Reduction of levels of infiltrating immune cells and less pronounced mucosal damage Enhancement of regulatory T cells and increase of serum levels of lipopolysaccharide [LPS]-binding protein	[83]
Short bowel syndrome	40 weaned female piglets	Polymeric infant formula supplemented with bovine colostrum protein concentrate (13 g/kg), 8 weeks	Increase of levels of circulating insulin-like growth factor (IGF-1) and binding proteins Muscle hypertrophy	[84]
	35 weaned female piglets	Polymeric infant formula supplemented with bovine colostrum protein isolate (Intact™), 8 weeks	Improvement of intestinal adaptation after extensive small bowel resection Maintenance of normal weight gain and stool consistency Enhancement of morphological adaptation 8 weeks after surgery	[85]

BC: bovine colostrum; HBC: Hyperimmune bovine colostrum; ICU: intensive care unit; PBS: phosphate-buffered saline; HIV: human immunodeficiency virus; HRV: human rotavirus infection; NEC: necrotizing enterocolitis; NSAIDs: nonsteroidal anti-inflammatory drugs; LPS: lipopolysaccharide.

maintained five weeks after stopping BC supplementation, followed by significant weight gain.

A placebo-controlled clinical trial with 160 children assessed the effect of bovine colostrum on treating acute diarrhoea [22]. For one week, the treated group was supplemented with commercial bovine colostrum product (6 g of powdered colostrum diluted in 50 mL of water). The authors concluded that colostrum was effective in treating both viral and bacterial acute diarrhoea, as they observed a reduction in diarrhoea and vomiting frequency and duration in the test group. Based on this outcome, BC should be considered as adjuvant therapy to prevent diarrhoea-related complications.

Hyperimmune colostrum has also been researched for treating gastrointestinal disorders [67,98]. Tablets with hyperimmune colostrum (400 mg and 200 mg) were administered to subjects challenged with an enterotoxigenic *E. coli* (ETEC) strain. Hyperimmune bovine colostrum powder promoted significant protection against the development of diarrhoea in all treatment groups, although no antimicrobial activity was observed. The authors suggest that when taken before eating or

drinking contaminated food or drink, the hyperimmune bovine colostrum they obtained can protect travellers from symptomatic infection with ETEC [67].

Although the limited number of randomised controlled trials studying the role of BC in infectious diarrhoea, an important systematic search, with meta-analysis, concluded that BC products ameliorate clinical symptoms of infectious diarrhoea among children [99].

3.3. Gut-barrier malfunction

Non-steroidal anti-inflammatory drugs can increase intestinal permeability, a disorder known as "leaky gut syndrome", increasing the likelihood of damage to the intestine and the risk of developing inflammatory and autoimmune diseases. In turn, colostrum decreases intestinal permeability and can be used in conjunction with non-steroidal anti-inflammatory drugs, preventing gastric lesions induced by these drugs [61].

Eslamian et al. evaluated enteral supplementation with bovine colostrum in 70 patients admitted to the ICU in a randomised, double-blind, placebo-controlled study [62]. The measurements of endotoxin and zonulin (a physiological permeability regulator) plasma levels showed a decrease in intestinal permeability after a short period of colostrum-supplemented enteral feedings. Colostrum administration was also effectively reduced diarrhoea in patients treated with colostrum, although no other secondary outcomes (vomiting, abdominal distention, mortality, incidence of new severe sepsis) were significantly different between control and treated groups. Furthermore, BC enteral supplementation reduced 7 days in the median length of stay in ICU when compared to the control group.

Increased intestinal permeability can be excessively upregulated by intense physical activity; thus, it is commonly observed in elite athletes [100]. Hałasa and co-workers investigated the effect of colostrum administration on the intestinal permeability of 16 mixed martial arts fighters during the competitive season. They reported restoration of intestinal permeability to a normal limit within less than three weeks of relatively mild supplementation [63]. Similar results were reported in a double-blind crossover study when oral supplementation with 20 g/day of BC was given to healthy male regular exercisers for 14 days. Exercise-induced changes in gut permeability were reduced by approximately 80% if colostrum had been taken. The authors postulate that this possibly occurs through reducing of temperature-induced apoptosis and inducing of heat shock protein 70 (HSP70) expression [64].

Cell culture experiments with four colostrum processed products showed that only the industrially processed ones could improve small intestinal barrier integrity [6]. The authors suggest that industrial processing increased protein concentration, and treatment (ultrafiltration and spray-drying of pasteurised skim colostrum) possibly altered the protein structure, removed inhibitors, or released bioactive peptides. On the other hand, processing may have inactivated the active components capable of altering colon motility. Further *in vitro* and *in vivo* studies are needed, especially clinical trials with a larger number of participants and different clinical conditions. They will contribute to the elucidation of the bovine colostrum regulatory action on intestinal permeability.

3.4. Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is a severe gastrointestinal disease that mainly affects premature babies. It is related to low birth weight and gestational age, causing gastrointestinal complications, and leading to death. The action of colostrum components can be beneficial to developing intestinal microbiota and helping in the recovery from the disease [16,101].

The risk of NEC development in newborns is increased by a lack of maternal colostrum intake. A cohort study with 3420 newborn children found a significant association between the absence of colostrum feeding and the occurrence of symptoms of intestinal obstruction and neonatal necrotizing enterocolitis. Children who did not receive maternal colostrum shortly after birth were twice as likely to develop intestinal obstruction symptoms when compared to children in early breastfeeding [102]. These results reinforce the importance of maternal colostrum intake in the first hours of the newborn's life. The treatment of intestinal pediatric failure is challenging, and the early start of feeding is essential, being human milk the preferred choice in neonates [103]. However, breastfeeding is not always possible for several reasons, or the mothers' milk amount is not enough, which requires a well-established human milk bank network to process and provide human colostrum in situations where it is needed. According to Sanchez Luna et al., only a few milk banks are able to offer preterm human milk, colostrum and transitional preterm milk from donors [104].

Therefore, scientific evidence must be gathered to certify bovine colostrum as an alternative to prevent NEC's deadly outcomes and to strengthen the newborn and premature babies' immune systems, protecting them from developing other diseases. In animal experiments with NEC in piglets, both human milk and bovine colostrum were effective in maturing intestinal function, structure, and resistance against this severe condition [68]. Another study carried out with preterm pigs showed that BC effectively restored intestinal functions after inflammation induced by NEC [69].

The use of prophylactic enteral bovine colostrum in very low birth weight neonates was evaluated in a blinded, parallel-group, stratified, randomised block, placebo-controlled trial [105]. BC administration showed a trend toward increased stool interleukin-6 and features of NEC. Due to the small sample size, the authors were unable to detect clinical benefits. They also highlight the importance of assessing the safety of this treatment since BC has a large number of proteins, which could potentially increase intestinal inflammation. The osmolarity of BC was identified as an essential measurement for future studies.

Human milk fortification with BC, also in animal experimentation, achieved superior performance in terms of gut function and health compared to formula fortification. The authors reported a reduction of diarrhoea and NEC incidence and modulation of gut permeability and cytokine levels in the human milk + BC group. BC was linked to the promotion of gut microbial homeostasis and preservation of barrier function [70].

In a prospective, randomised, placebo-controlled, double-blinded trial, 80 preterm infants were divided into two groups (BC or placebo). Intending to evaluate whether gut priming with bovine colostrum reduces nosocomial sepsis episodes, feeding intolerance and necrotizing enterocolitis (NEC) in premature infants, the authors concluded BC could be recommended for gut priming. None of the BC fed infants developed NEC, and significant reduction of mortality and feeding intolerance were registered [71].

Since BC could help improve the survival rate of premature babies, its efficacy and safety in human newborn feeding are worth more attention. The FortiColos multicentre study is expected to provide important data in this regard [106]. Even though BC composition differs from human colostrum, BC products could help to provide appropriate nutrition, especially to preterm infants who do not have access to breastfeeding or colostrum and milk from a human milk bank.

3.5. Drug-induced lesions

Anti-inflammatory drugs are widely used to treat injuries. However, long-term use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) can provoke harmful effects in the GIT [77]. More than two decades ago, Playford et al. demonstrated the *in vitro* (human colonic carcinoma cells HT-29) and *in vivo* (mice) protection conferred by colostrum against injuries caused by the NSAID indomethacin [72]. Later, in a study conducted with humans, the same research group evaluated healthy subjects' intestinal permeability of upon the use of anti-inflammatory drugs. Indomethacin increased intestinal permeability by three times, while there was no increase in permeability in

volunteers who ingested colostrum together with the drug [77]. Mir et al. found that the C-terminal half of lactoferrin (C-lobe) purified from bovine colostrum has an affinity with NSAIDs, which can be responsible for the damage prevention provided by BC consumption [74].

Animal studies have observed comparable results. The effects of the combined use of colostrum with anti-inflammatory drugs to reduce damage in GIT was investigated in mice. A single dose of diclofenac was administered to induce the damage, while different colostrum proportions were used to assess the protective potential against injury. As a result, there were decreases in intestinal permeability and damages to the intestinal villi and reduction of bacterial growth [73]. An important study conducted to compare commercially available BC products found beneficial effects of BC in gastric mucosa restoration, promoting cell proliferation and cell migration [15]. In piglets under chemotherapy, lower levels of inflammatory markers and greater intestinal enzyme activity were attributed to BC intake, which acted in reducing intestinal drug toxicity [75]. After another experiment using piglets, Martin and co-workers concluded that colostrum could be used to preventively reduce the damage caused by lesions from chemotherapy [76].

The symptoms of oral mucositis were reduced by a commercially available toothpaste containing lysozyme, lactoferrin, lactoperoxidase and colostrum purified extract. Pediatric patients with chemotherapy-related oral mucositis experienced significantly better oral hygiene. The results were attributed to BC antibacterial properties and mild anti-inflammatory effect (due to the antioxidant components), which allowed greater accuracy and tolerance to cleaning procedures as well as more time spent on oral hygiene [107].

The use of enteral supplementation with bovine colostrum was investigated in patients with acute lymphoblastic leukaemia and no beneficial effects were observed in the primary outcome (number of days with fever) [108]. On the other hand, the peak of oral mucositis severity was significantly lower in the colostrum group than in the placebo group, although BC administration did not diminish intestinal mucositis. The results suggest a possible protective effect of BC on the oral mucosa.

3.6. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of diseases that affect the intestine, classified by two main phenotypes: ulcerative colitis and Crohn's disease. Its causes have not yet been clarified, but studies suggest that they can be caused by intestinal mucosa immune system dysfunction. Hence, bovine colostrum is posed as an alternative to supply immune factors and growth factors, able to assist in recovering the GIT [16,109].

BC and its bioactive constituents have shown to be possibly used to alleviate the clinical course of inflammatory diseases, such as IBD [110]. An investigation about the *in vitro* anti-inflammatory and antibacterial effects of colostrum on intestinal cells showed the benefits of BC to intestinal health. A decrease in the inflammatory response and low bacterial adhesion to cells were observed [111].

Animal studies, using different models of induced colitis in mice, demonstrated that BC supplementation reduces intestinal damages. The prophylactic administration of BC resulted in lower clinical severity, less weight loss, and decreased colorectal inflammation compared to the control group [79]. Another study tested the effectiveness of bovine colostrum, immunoglobulin A and lactoferrin alone in preventing and treating induced colitis in mice. Mice received treatments two weeks before induction or after showing symptoms of the disease. Colostrum helped the recover from colitis after the initial injury, but there was no recovery of the lost weight. On the other hand, lactoferrin administration had no effect on these variables, whereas IgA improved the immune cell response and promoted weight gain in therapeutic treatment but did not improve the clinical condition [80].

Menchetti and coworkers observed a reduction in inflammatory markers and modulation of intestinal microbiota when evaluating bovine colostrum administration for seven days as a prophylactic measure to reduce colitis induced in mice. BC was reported to be responsible for stimulating the growth of *Bifidobacterium* spp. and *Lactobacillus* spp., considered beneficial colonic microorganisms [81]. Similar conclusions on the role of BC in preventing intestinal damage and signs of colitis in mice had been reached earlier. The study registered downregulation of toll-like receptor 4 (TLR4) and cytokine expression, reduction of body weight loss and histological score and preservation of beneficial intestinal microbiota. BC administration was well tolerated and did not induce damages or pathological symptoms [82].

The use of a hyperimmune colostrum-based product was effective in ameliorating colitis in two mechanistically different mouse models of intestinal inflammation [83]. The mechanism of action of the bioactive components remains unknown, but it might be related to the formation of immune complexes of IgG with microbial lipopolysaccharides, reducing the inflammatory responses. The authors suggest the hyperimmune colostrum-based product might be a promising novel therapeutic agent in IBD, to be used alone, for maintaining remission in mild colitis cases, or combined with other treatments, aiming to enhance the therapeutic efficacy.

The potential beneficial effects of BC on inflammatory bowel diseases must be investigated with randomised placebo-controlled clinical trials. Well-designed studies will help to draft conclusions regarding BC application as a treatment for these conditions. They will provide a better understanding of which BC components modulate the inflammatory process and could subside the development of administration protocols, appropriate for each type of disease, according to the patients' clinical status. Potential contraindications also need to be studied.

3.7. Short bowel syndrome

Short bowel syndrome is an intestinal insufficiency resulting from intestine resection due to infarction of the mesenteric vessels, trauma, abnormalities, or complications of Crohn's disease. It is characterised by diarrhoea and low nutrient absorption, with consequent malnutrition and weight loss [112].

Pereira-Fantini and co-workers obtained promising results when analysing colostrum protein concentrate supplementation in piglets. Supplementation resulted in muscle hypertrophy, increased levels of circulating insulin-like growth factor (IGF-1) and binding proteins. The findings indicate that supplementation with colostrum protein concentrate may be an alternative for treating short bowel syndrome [84]. Although no evidence of small bowel adaptation when using a diet with IGF-1 enriched colostrum in piglets was found [113], normal weight gain and stool normalisation were observed in animals with massive small bowel resection when treated with colostrum protein concentrate. Increased villus length and crypt depth in intestinal epithelium are morphological features of intestinal adaptation, which was improved by BC protein concentrate supplementation [85].

Conversely, clinical trials found no differences in colostrum administration compared to placebo in patients with short bowel syndrome [114,115]. Considering that both studies were carried out with a very small population (twelve and nine volunteers), further research is needed to investigate the effect of BC in short bowel syndrome symptoms in humans and confirm the results reported so far. The potential benefits of BC or its isolated bioactive compounds in short bowel syndrome treatment remain uncertain.

4. Conclusion

Bovine colostrum has a unique combination of nutrients and bioactive compounds, making it a natural supplement or source of molecules for high added-value nutraceutical foods and products. BC intake can improve gastrointestinal symptoms related to several disorders and diseases thank important attributes, such as protection against pathogenic microbial growth, enhancement of beneficial microbiota,

reduction of endotoxemia, modulation of the immune response, stimulation of growth and repair of damaged intestinal tissues and restoration of gut permeability. Therefore, BC consumption might be a valuable prevention factor or treatment for various conditions where gastrointestinal tract function is impaired.

Although there is evidence of the role of BC in maintaining and restoring intestinal health, further investigations should be focused on better understanding the mechanisms of action involved in the protective effect of bovine colostrum on the gastrointestinal tract. Moreover, monitoring the industrial-scale processing methods is essential to preserve the integrity of the biologically active molecules in BC products. These molecules have been reported as the key for the unique properties of BC therefore, the influence of gastrointestinal environment conditions and interaction with intestinal microbiota may drastically change BC efficacy according to the amount and form of administration. Future investigations must be carried out in this direction since the physiopathology of GIT disorders is very distinct, which requires different therapeutic and/or preventive approaches.

Funding sources

This research was supported by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)*, Brazilian Ministry of Education.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

References

[1] P. Marnila, H. Korhonen, Milk | Colostrum, in: J. Fuquay (Ed.), Encycl. Dairy Sci, Academin Press, San Diego, 2011, pp. 591–597, https://doi.org/10.1016/B978-0-12-374407-4.00322-8.
[2] E. Mizelman, W. Duff, S. Kontulainen, P.D. Chilibeck, The Health Benefits of Bovine Colostrum, 2017, https://doi.org/10.1016/B978-0-12-809762-5.00004-8.
[3] M. Ross, H. Atalla, N. Karrow, B.A. Mallard, The bioactivity of colostrum and milk exosomes of high, average, and low immune responder cows on human intestinal epithelial cells, J. Dairy Sci. 104 (2021), https://doi.org/10.3168/jds.2020-18405.
[4] R. Mehra, R. Singh, V. Nayan, H.S. Buttar, N. Kumar, S. Kumar, et al., Nutritional attributes of bovine colostrum components in human health and disease: a comprehensive review, Food Biosci. 40 (2021), https://doi.org/10.1016/j.fbio.2021.100907.
[5] D.A. Moore, J. Taylor, M.L. Hartman, W.M. Sischo, Quality assessments of waste milk at a calf ranch, J. Dairy Sci. 92 (2009), https://doi.org/10.3168/jds.2008-1623.
[6] R.C. Anderson, J.E. Dalziel, N.W. Haggarty, K.E. Dunstan, P.K. Gopal, N.C. Roy, Short communication: Processed bovine colostrum milk protein concentrate increases epithelial barrier integrity of Caco-2 cell layers, J. Dairy Sci. 102 (2019), https://doi.org/10.3168/jds.2019-16951.
[7] D.E.W. Chatterton, S. Aagaard, T. Hesselballe Hansen, D.N. Nguyen, C. De Gobba, R. Lametsch, et al., Bioactive proteins in bovine colostrum and effects of heating, drying and irradiation, Food Funct. 11 (2020) 2309–2327, https://doi.org/10.1039/c9fo02998b.
[8] W. Xu, S. Mann, G. Curone, Kenéz, Heat treatment of bovine colostrum: effects on colostrum metabolome and serum metabolome of calves, Animal. 15 (2021), https://doi.org/10.1016/j.animal.2021.100180.
[9] D.N. Nguyen, A.J. Currie, S. Ren, S.B. Bering, P.T. Sangild, Heat treatment and irradiation reduce anti-bacterial and immune-modulatory properties of bovine colostrum, J. Funct. Foods 57 (2019), https://doi.org/10.1016/j.jff.2019.04.012.
[10] A.C.F. Støy, P.T. Sangild, K. Skovgaard, T. Thymann, M. Bjerre, D.E. W. Chatterton, et al., Spray dried, pasteurised bovine colostrum protects against gut dysfunction and inflammation in Preterm Pigs, J. Pediatr. Gastroenterol. Nutr. 63 (2016).
[11] S.G. Borad, A.K. Singh, G.S. Meena, H.V. Raghu, Storage related changes in spray dried colostrum preparations, LWT. 118 (2020), https://doi.org/10.1016/j.lwt.2019.108719.
[12] S.G. Borad, A.K. Singh, Colostrum immunoglobulins: processing, preservation and application aspects, Int. Dairy J. 85 (2018) 201–210, https://doi.org/10.1016/j.idairyj.2018.05.016.
[13] S.G. Borad, A.K. Singh, G.S. Meena, S. Arora, P.N. Raju, L. Sabikhi, Optimization of spray drying of colostrum protein ingredients–A rheological approach, J. Food Eng. 288 (2021), https://doi.org/10.1016/j.jfoodeng.2020.110247.
[14] S. Sotudeh, M. Rabbani Khorasgani, Z. Etemadifar, S.H. Zarkesh-Esfahani, Effects of spray-drying, freeze-drying and pasteurization on microbiological quality and IgG level of bovine colostrum, J. Food Qual. Hazards Control. 5 (2018), https://doi.org/10.29252/jfqhc.5.2.5.
[15] R.J. Playford, M. Cattell, T. Marchbank, Marked variability in bioactivity between commercially available bovine colostrum for human use; implications for clinical trials, PLoS One 15 (2020), https://doi.org/10.1371/journal.pone.0234719.
[16] L. Menchetti, G. Traina, G. Tomasello, P. Casagrande-Proietti, L. Leonardi, O. Barbato, et al., Potential benefits of colostrum in gastrointestinal diseases, Front. Biosci. - Sch. 8 (2016) 331–351, https://doi.org/10.2741/s467.
[17] G. Davison, A.W. Jones, T. Marchbank, R.J. Playford, Oral bovine colostrum supplementation does not increase circulating insulin-like growth factor-1 concentration in healthy adults: results from short- and long-term administration studies, Eur. J. Nutr. 59 (2020), https://doi.org/10.1007/s00394-019-02004-6.
[18] H.S. Buttar, S.M. Bagwe, S.K. Bhullar, G. Kaur, Health benefits of bovine colostrum in children and adults, in: Dairy Hum. Heal. Dis. across Lifesp, 2017, https://doi.org/10.1016/B978-0-12-809868-4.00001-7.
[19] S. Dzik, B. Miciński, I. Aitzhanova, J. Miciński, J. Pogorzelska, A. Beisenov, et al., Properties of bovine colostrum and the possibilities of use, Polish Ann. Med. 24 (2017), https://doi.org/10.1016/j.poamed.2017.03.004.
[20] M.H. Saalfeld, D.I..B. Pereira, K.R.K. Silveira, G.L. Diniz, D.H. Kringel, M.I. Alves, et al., Colostro: a redescoberta de um alimento saudável, nutritivo e com potencial probiótico, Agroecol. e Desenvolv. Rural Sustentáve. 2 (2012) 18–24.
[21] O. Perdijk, M. van Splunter, H.F.J. Savelkoul, S. Brugman, R.J.J. van Neerven, et al., Front. Immunol. 9 (2018), https://doi.org/10.3389/fimmu.2018.00143.
[22] S.H. Barakat, M.A. Meheissen, O.M. Omar, D.A. Elbana, Bovine colostrum in the treatment of acute diarrhea in children: a double-blinded randomized controlled trial, J. Trop. Pediatr. 66 (2019), https://doi.org/10.1093/tropej/fmz029.
[23] A. Batista da Silva Galdino, A.H. do Nascimento Rangel, H.S. Buttar, M. Sales Lima Nascimento, E. Cristina Gavioli, R.P. de Oliveira, et al., Bovine colostrum: benefits for the human respiratory system and potential contributions for clinical management of COVID-19, Food Agric. Immunol. 32 (2021), https://doi.org/10.1080/09540105.2021.1892594.
[24] P.T. Sangild, C. Vonderohe, V. Melendez Hebib, D.G. Burrin, Potential benefits of bovine colostrum in pediatric nutrition and health, Nutrients. 13 (2021) 1–41, https://doi.org/10.3390/nu13082551.
[25] A. Arslan, M. Kaplan, H. Duman, A. Bayraktar, M. Ertürk, B.M. Henrick, et al., Bovine colostrum and its potential for human health and nutrition, Front. Nutr. 8 (2021) 1–12, https://doi.org/10.3389/fnut.2021.651721.
[26] E. Mouton, K.J. Aryana, Influence of colostrum on the characteristics of ice cream, Food Nutr. Sci. 06 (2015), https://doi.org/10.4236/fns.2015.65049.
[27] M.H. Saalfeld, D.I.B. Pereira, J.D.S.S. Valente, J.L. Borchardt, C.F. Weissheimer, M.A. Gularte, et al., Efeito da fermentação anaeróbica do colostro bovino na inibição do crescimento de bactérias, Cienc. Rural. 46 (2016), https://doi.org/10.1590/0103-8478cr20160393.
[28] T. Miyazaki, K. Okada, M. Miyazaki, Short communication: neonatal calves coagulate first-milking colostrum and produce a large curd for efficient absorption of immunoglobulins after first ingestion, J. Dairy Sci. 100 (2017), https://doi.org/10.3168/jds.2017-12808.
[29] A.S. Abdel-Ghany, D.A. Zaki, Production of novel functional yoghurt fortified with bovine colostrum and date syrup for children, Alexandria Sci. Exch. J. 39 (2018), https://doi.org/10.21608/asejaiqjsae.2018.20475.
[30] S. Bagwe, L.J.P. Tharappel, G. Kaur, H.S. Buttar, Bovine colostrum: An emerging nutraceutical, J. Complement. Integr. Med. 12 (2015), https://doi.org/10.1515/jcim-2014-0039.
[31] B.A. McGrath, P.F. Fox, P.L.H. McSweeney, A.L. Kelly, Composition and properties of bovine colostrum: a review, Dairy Sci. Technol. 96 (2016) 133–158, https://doi.org/10.1007/s13594-015-0258-x.
[32] E. Bartkiene, V. Bartkevics, L.E. Ikkere, I. Pugajeva, P. Zavistanaviciute, V. Lele, et al., The effects of ultrasonication, fermentation with Lactobacillus sp., and dehydration on the chemical composition and microbial contamination of bovine colostrum, J. Dairy Sci. 101 (2018), https://doi.org/10.3168/jds.2018-14692.
[33] S.M. Godden, J.E. Lombard, A.R. Woolums, Colostrum management for dairy calves, Vet. Clin. North Am. - Food Anim. Pract. 35 (2019), https://doi.org/10.1016/j.cvfa.2019.07.005.
[34] S. Hasan, T. Orro, A. Valros, S. Junnikkala, O. Peltoniemi, C. Oliviero, Factors affecting sow colostrum yield and composition, and their impact on piglet growth and health, Livest. Sci. 227 (2019), https://doi.org/10.1016/j.livsci.2019.07.004.
[35] H.J. Korhonen, Production and properties of health-promoting proteins and peptides from bovine colostrum and milk, Cell. Mol. Biol. 58 (2012) 26–38, https://doi.org/10.1170/T915.
[36] D.J. Atkinson, M.A.G. von Keyserlingk, D.M. Weary, Benchmarking passive transfer of immunity and growth in dairy calves, J. Dairy Sci. 100 (2017), https://doi.org/10.3168/jds.2016-11800.
[37] W.L. Hurley, P.K. Theil, Perspectives on immunoglobulins in colostrum and milk, Nutrients. 3 (2011), https://doi.org/10.3390/nu3040442.
[38] S.I. Kehoe, B.M. Jayarao, A.J. Heinrichs, A survey of bovine colostrum composition and colostrum management practices on Pennsylvania dairy farms, J. Dairy Sci. 90 (2007), https://doi.org/10.3168/jds.2007-0040.
[39] S. Feeney, S.T. Morrin, L. Joshi, R.M. Hickey, The role of immunoglobulins from bovine colostrum and milk in human health promotion, in: Nov. Proteins Food, Pharm. Agric, 2018, https://doi.org/10.1002/9781119385332.ch16.
[40] D. Legrand, E. Elass, M. Carpentier, J. Mazurier, Lactoferrin: a modulator of immune and inflammatory responses, Cell. Mol. Life Sci. 62 (2005), https://doi.org/10.1007/s00018-005-5370-2.

[41] A. Aboda, W. Taha, I. Attia, A. Gad, M. Mahmoud Mostafa, M. Abdelfattah Abdelwadod, et al., Iron bond bovine lactoferrin for the treatment of cancers and anemia associated with cancer cachexia, Adv. Ave. Dev. Nov. Carriers Bioact. Biol. Agents (2020), https://doi.org/10.1016/b978-0-12-819666-3.00008-0.

[42] P. Manzoni, Clinical studies of lactoferrin in neonates and infants: an update, Breastfeed. Med. 14 (2019), https://doi.org/10.1089/bfm.2019.0033.

[43] D. Legrand, Overview of lactoferrin as a natural immune modulator, J. Pediatr. 173 (2016), https://doi.org/10.1016/j.jpeds.2016.02.071.

[44] H.J. Korhonen, Bioactive milk proteins, peptides and lipids and other functional components derived from milk and bovine colostrum, in: Funct. Foods Concept to Prod, Second Ed, 2011, https://doi.org/10.1533/9780857092557.3.471.

[45] A. Akbache, É. Lamiot, O. Moroni, S. Turgeon, S.F. Gauthier, Y. Pouliot, Use of membrane processing to concentrate TGF-β2 and IGF-I from bovine milk and whey, J. Membr. Sci. 326 (2009), https://doi.org/10.1016/j.memsci.2008.10.026.

[46] M. Fernández, J.A. Hudson, R. Korpela, C.G. De Los Reyes-Gavilán, Impact on human health of microorganisms present in fermented dairy products: an overview, Biomed. Res. Int. 2015 (2015), https://doi.org/10.1155/2015/412714.

[47] M. García-Burgos, J. Moreno-Fernández, M.J.M. Alférez, J. Díaz-Castro, I. López-Aliaga, New perspectives in fermented dairy products and their health relevance, J. Funct. Foods 72 (2020), https://doi.org/10.1016/j.jff.2020.104059.

[48] A.W. Jones, D.S. March, F. Curtis, C. Bridle, Bovine colostrum supplementation and upper respiratory symptoms during exercise training: a systematic review and meta-analysis of randomised controlled trials, BMC Sports Sci. Med. Rehabil. 8 (2016), https://doi.org/10.1186/s13102-016-0047-8.

[49] E.G.S.O. dos Silva, A.H.N. do Rangel, L. Mürmam, M.F. Bezerra, J.P.F. de Oliveira, E.G.S.O. dos Silva, et al., Bovine colostrum: benefits of its use in human food, Food Sci. Technol. 39 (2019) 355–362, https://doi.org/10.1590/fst.14619.

[50] K. Saad, M.G.M. Abo-Elela, K.A.A. El-Baseer, A.E. Ahmed, F.A. Ahmad, M.S. K. Tawfeek, et al., Effects of bovine colostrum on recurrent respiratory tract infections and diarrhea in children, Med. (United States). 95 (2016), https://doi.org/10.1097/MD.0000000000004560.

[51] M.J. An, J.H. Cheon, S.W. Kim, J.J. Park, C.M. Moon, S.Y. Han, et al., Bovine colostrum inhibits nuclear factor κB-mediated proinflammatory cytokine expression in intestinal epithelial cells, Nutr. Res. 29 (2009), https://doi.org/10.1016/j.nutres.2009.03.011.

[52] M.R. Sanctuary, J.N. Kain, S.Y. Chen, K. Kalanetra, D.G. Lemay, D.R. Rose, et al., Pilot study of probiotic/colostrum supplementation on gut function in children with autism and gastrointestinal symptoms, PLoS One 14 (2019), https://doi.org/10.1371/journal.pone.0210064.

[53] S. Larcombe, M.L. Hutton, D. Lyras, Hyperimmune bovine colostrum reduces gastrointestinal carriage of uropathogenic *Escherichia coli*, Hum. Vac. Immunother. 15 (2019), https://doi.org/10.1080/21645515.2018.1528836.

[54] S. Sugiharto, A.S.R. Poulsen, N. Canibe, C. Lauridsen, Effect of bovine colostrum feeding in comparison with milk replacer and natural feeding on the immune responses and colonisation of enterotoxigenic *Escherichia coli* in the intestinal tissue of piglets, Br. J. Nutr. 113 (2015), https://doi.org/10.1017/S0007114514003201.

[55] J.K. Sponseller, J.A. Steele, D.J. Schmidt, H.B. Kim, G. Beamer, X. Sun, et al., Hyperimmune bovine colostrum as a novel therapy to combat *clostridium difficile* infection, in: J. Infect. Dis, 2015, https://doi.org/10.1093/infdis/jiu605.

[56] J.R. Döhler, L. Nebermann, Bovine colostrum in oral treatment of enterogenic endotoxaemia in rats, Crit. Care 6 (2002), https://doi.org/10.1186/cc1819.

[57] E. Bölke, P.M. Jehle, F. Hausmann, A. Däubler, H. Wiedeck, G. Steinbach, et al., Preoperative oral application of immunoglobulin-enriched colostrum milk and mediator response during abdominal surgery, Shock. 17 (2002), https://doi.org/10.1097/00024382-200201000-00002.

[58] C.D. Tran, S. Kritas, M.A.F. Campbell, H.Q. Huynh, S.S. Lee, R.N. Butler, Novel combination therapy for the eradication of *Helicobacter pylori* infection in a mouse model, Scand. J. Gastroenterol. 45 (2010), https://doi.org/10.3109/00365521.2010.506245.

[59] T.H. Casswall, H.O. Nilsson, L. Björck, S. Sjöstedt, L. Xu, C.E. Nord, et al., Bovine anti-*Helicobacter pylori* antibodies for oral immunotherapy, Scand. J. Gastroenterol. 37 (2002), https://doi.org/10.1080/003655202762671242.

[60] F. Megahed, M. El-Assal, A. Dabour, R. Samy, M. Rizk, S. Al Adhm, Lactoferrin as an added therapy in the treatment of *Helicobacter pylori*, Benha Med. J. 34 (2017), https://doi.org/10.4103/bmfj.bmfj_25_17.

[61] Z. Khan, C. Macdonald, A.C. Wicks, M.P. Holt, D. Floyd, S. Ghosh, et al., Use of the "nutriceutical", bovine colostrum, for the treatment of distal colitis: results from an initial study, Aliment. Pharmacol. Ther. 16 (2002), https://doi.org/10.1046/j.1365-2036.2002.01354.x.

[62] G. Eslamian, S.H. Ardehali, A.R. Baghestani, Z. Vahdat Shariatpanahi, Effects of early enteral bovine colostrum supplementation on intestinal permeability in critically ill patients: a randomized, double-blind, placebo-controlled study, Nutrition. 60 (2019), https://doi.org/10.1016/j.nut.2018.10.013.

[63] M. Hałasa, D. Maciejewska, M. Baśkiewicz-Hałasa, B. Machaliński, K. Safranow, E. Stachowska, Oral supplementation with bovine colostrum decreases intestinal permeability and stool concentrations of Zonulin in athletes, Nutrients. 9 (2017) 1–11, https://doi.org/10.3390/nu9040370.

[64] T. Marchbank, G. Davison, J.R. Oakes, M.A. Ghatei, M. Patterson, M.P. Moyer, et al., The nutriceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes, Am. J. Physiol. Gastrointest. Liver Physiol. 300 (2011), https://doi.org/10.1152/ajpgi.00281.2010.

[65] F.O. Kaducu, S.A. Okia, G. Upenytho, L. Elfstrand, C.H. Florén, Effect of bovine colostrum-based food supplement in the treatment of HIV-associated diarrhea in Northern Uganda: a randomized controlled trial, Indian J. Gastroenterol. 30 (2011), https://doi.org/10.1007/s12664-011-0146-0.

[66] M. Inagaki, M. Yamamoto, Xijier Cairangzhuoma, T. Yabe, K. Uchida, et al., Multiple-dose therapy with bovine colostrum confers significant protection against diarrhea in a mouse model of human rotavirus-induced gastrointestinal disease, J. Dairy Sci. 96 (2013), https://doi.org/10.3168/jds.2012-5847.

[67] W. Otto, B. Najnigier, T. Stelmasiak, R.M. Robins-Browne, Randomized control trials using a tablet formulation of hyperimmune bovine colostrum to prevent diarrhea caused by enterotoxigenic *Escherichia coli* in volunteers, Scand. J. Gastroenterol. 46 (2011), https://doi.org/10.3109/00365521.2011.574726.

[68] M.L. Jensen, P.T. Sangild, M. Lykke, M. Schmidt, M. Boye, B.B. Jensen, et al., Similar efficacy of human banked milk and bovine colostrum to decrease incidence of necrotizing enterocolitis in preterm piglets, Am. J. Phys. Regul. Integr. Comp. Phys. 305 (2013), https://doi.org/10.1152/ajpregu.00094.2013.

[69] A.C.F. Stoy, P.T. Sangild, K. Skovgaard, T. Thymann, M. Bjerre, D.E. W. Chatterton, et al., Bovine colostrum maintains its protective effects against necrotizing enterocolitis in preterm pigs after spray drying and pasteurization, J. Parenter. Enter. Nutr. (2013) 1–34.

[70] J. Sun, Y. Li, X. Pan, D.N. Nguyen, A. Brunse, A.M. Bojesen, et al., Human milk fortification with bovine colostrum is superior to formula-based fortifiers to prevent gut dysfunction, necrotizing enterocolitis, and systemic infection in preterm pigs, J. Parenter. Enter. Nutr. 43 (2019), https://doi.org/10.1002/jpen.1422.

[71] R.I.H. Ismail, H.A. Awad, S.S. Imam, G.I. Gad, N.M. Aboushady, R.M. Abdou, et al., Gut priming with bovine colostrum and T regulatory cells in preterm neonates: a randomized controlled trial, Pediatr. Res. (2020), https://doi.org/10.1038/s41390-020-01344-y.

[72] R.J. Playford, D.N. Floyd, C.E. Macdonald, D.P. Calnan, R.O. Adenekan, W. Johnson, et al., Bovine colostrum is a health food supplement which prevents NSAID induced gut damage, Gut. 44 (1999), https://doi.org/10.1136/gut.44.5.653.

[73] J.W. Kim, W.K. Jeon, J.W. Yun, D. Il Park, Y.K. Cho, I.K. Sung, et al., Protective effects of bovine colostrum on non-steroidal anti-inflammatory drug induced intestinal damage in rats, Asia Pac. J. Clin. Nutr. 14 (2005).

[74] R. Mir, N. Singh, G. Vikram, R.P. Kumar, M. Sinha, A. Bhushan, et al., The structural basis for the prevention of nonsteroidal antiinflammatory drug-induced gastrointestinal tract damage by the C-lobe of bovine colostrum lactoferrin, Biophys. J. 97 (2009), https://doi.org/10.1016/j.bpj.2009.09.030.

[75] P.E.L. Pontoppidan, R.L. Shen, M.S. Cilieborg, P. Jiang, H. Kissow, B.L. Petersen, et al., Bovine colostrum modulates myeloablative chemotherapy-induced gut toxicity in piglets, J. Nutr. 145 (2015), https://doi.org/10.3945/jn.114.203430.

[76] J. Martin, S.C. Howard, A. Pillai, P. Vogel, A.P. Naren, S. Davis, et al., The weaned pig as a model for doxorubicin-induced mucositis, Chemotherapy. 60 (2014), https://doi.org/10.1159/000365725.

[77] R.J. Playford, C.E. Macdonald, D.P. Calnan, D.N. Floyd, T. Podas, W. Johnson, et al., Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability, Clin. Sci. 100 (2001), https://doi.org/10.1042/CS20010015.

[78] M. Rathe, S. De Pietri, P.S. Wehner, T.L. Frandsen, K. Grell, K. Schmiegelow, et al., Bovine colostrum against chemotherapy-induced gastrointestinal toxicity in children with acute lymphoblastic leukemia: a randomized, double-blind, placebo-controlled trial, J. Parenter. Enter. Nutr. 44 (2020) 337–347, https://doi.org/10.1002/jpen.1528.

[79] P. Bodammer, C. Maletzki, G. Waitz, J. Emmrich, Prophylactic application of bovine colostrum ameliorates murine colitis via induction of immunoregulatory cells, J. Nutr. 141 (2011), https://doi.org/10.3945/jn.110.128702.

[80] P. Bodammer, E. Zirzow, S. Klammt, C. Maletzki, C. Kerkhoff, Alteration of DSS-mediated immune cell redistribution in murine colitis by oral colostral immunoglobulin, BMC Immunol. 14 (2013), https://doi.org/10.1186/1471-2172-14-10.

[81] L. Menchetti, G. Curone, I.E. Filipescu, O. Barbato, L. Leonardi, G. Guelfi, et al., The prophylactic use of bovine colostrum in a murine model of TNBS-induced colitis, Animals. 10 (2020), https://doi.org/10.3390/ani10030492.

[82] I.E. Filipescu, L. Leonardi, L. Menchetti, G. Guelfi, G. Traina, P. Casagrande-Proietti, et al., Preventive effects of bovine colostrum supplementation in TNBS-induced colitis in mice, PLoS One 13 (2018) 1–17, https://doi.org/10.1371/journal.pone.0202929.

[83] M.R. Spalinger, K. Atrott, K. Baebler, M. Schwarzfischer, H. Melhem, D.R. Peres, et al., Administration of the hyper-immune bovine colostrum extract IMM-124E ameliorates experimental murine colitis, J. Crohn's Colitis 13 (2019), https://doi.org/10.1093/ecco-jcc/jjy213.

[84] P.M. Pereira-Fantini, S.L. Thomas, R.G. Taylor, E. Nagy, M. Sourial, P.J. Fuller, et al., Colostrum supplementation restores insulin-like growth factor −1 levels and alters muscle morphology following massive small bowel resection, J. Parenter. Enter. Nutr. 32 (2008), https://doi.org/10.1177/0148607108316197.

[85] È.S. Nagy, M.C.J. Paris, R.G. Taylor, P.J. Fuller, M. Sourial, F. Justice, et al., Colostrum protein concentrate enhances intestinal adaptation after massive small bowel resection in juvenile pigs, J. Pediatr. Gastroenterol. Nutr. 39 (2004) 487–492, https://doi.org/10.1097/00005176-200411000-00008.

[86] R. Yadav, T. Angolkar, G. Kaur, H.S. Buttar, Antibacterial and antiinflammatory properties of bovine colostrum, Recent Patents Inflamm. Allergy Drug Discov. 10 (2016), https://doi.org/10.2174/1872214810666160219163118.

[87] A. Civra, A. Altomare, R. Francese, M. Donalisio, G. Aldini, D. Lembo, Colostrum from cows immunized with a veterinary vaccine against bovine rotavirus displays enhanced in vitro anti-human rotavirus activity, J. Dairy Sci. 102 (2019), https://doi.org/10.3168/jds.2018-16016.

[88] E. Bartkiene, M. Ruzauskas, V. Lele, P. Zavistanaviciute, J. Bernatoniene, V. Jakstas, et al., Development of antimicrobial gummy candies with addition of bovine colostrum, essential oils and probiotics, Int. J. Food Sci. Technol. 53 (2018), https://doi.org/10.1111/ijfs.13701.
[89] E. Bartkiene, V. Lele, V. Sakiene, P. Zavistanaviciute, M. Ruzauskas, A. Stankevicius, et al., Fermented, ultrasonicated, and dehydrated bovine colostrum: changes in antimicrobial properties and immunoglobulin content, J. Dairy Sci. 103 (2020) 1315–1323, https://doi.org/10.3168/jds.2019-16357.
[90] D. Berger, U.M. Schmidt, S. Ott, M. Seidelmann, R. Martin, H.G. Beger, Incidence and pathophysiological relevance of postoperative endotoxemia, FEMS Immunol. Med. Microbiol. 11 (1995), https://doi.org/10.1016/0928-8244(95)00036-7.
[91] K. Orth, W.T. Knoefel, M. Van Griensven, C. Matuschek, M. Peiper, H. Schrumpf, et al., Preventively enteral application of immunoglobulin enriched colostrums milk can modulate postoperative inflammatory response, Eur. J. Med. Res. 18 (2013), https://doi.org/10.1186/2047-783X-18-50.
[92] S. Suerbaum, P. Michetti, Helicobacter pylori infection, N. Engl. J. Med. 347 (2002) 1175–1186.
[93] C.Y. Kao, B.S. Sheu, J.J. Wu, *Helicobacter pylori* infection: an overview of bacterial virulence factors and pathogenesis, Biom. J. 39 (2016), https://doi.org/10.1016/j.bj.2015.06.002.
[94] P. Malfertheiner, F. Megraud, C. O'Morain, J.P. Gisbert, E.J. Kuipers, A. Axon, et al., Management of *helicobacter pylori* infection-the Maastricht V/Florence consensus report, Gut. 66 (2017), https://doi.org/10.1136/gutjnl-2016-312288.
[95] J. Parsonnet, H. Shmuely, T. Haggerty, Fecal and oral shedding of Helicobacter pylori from healthy infected adults, J. Am. Med. Assoc. 282 (1999) 2240–2245, https://doi.org/10.1001/jama.282.23.2240.
[96] M.M. Bitzan, B.D. Gold, D.J. Philpott, M. Huesca, P.M. Sherman, H. Karch, et al., Inhibition of *Helicobacter pylori* and *Helicobacter mustelae* binding to lipid receptors by bovine colostrum, J. Infect. Dis. 177 (1998), https://doi.org/10.1086/515256.
[97] P. Marnila, S. Rokka, L. Rehnberg-Laiho, P. Kärkkäinen, T.U. Kosunen, H. Rautelin, et al., Prevention and suppression of *Helicobacter felis* infection in mice using colostral preparation with specific antibodies, Helicobacter. 8 (2003), https://doi.org/10.1046/j.1523-5378.2003.00144.x.
[98] J. Steele, J. Sponseller, D. Schmidt, O. Cohen, S. Tzipori, Hyperimmune bovine colostrum for treatment of GI infections, Hum. Vaccin. Immunother. 9 (2013), https://doi.org/10.4161/hv.24078.
[99] J. Li, Y.W. Xu, J.J. Jiang, Q.K. Song, Bovine colostrum and product intervention associated with relief of childhood infectious diarrhea, Sci. Rep. 9 (2019) 1–6, https://doi.org/10.1038/s41598-019-39644-x.
[100] M. Lamprecht, A. Frauwallner, Exercise, intestinal barrier dysfunction and probiotic supplementation, Med. Sport Sci. 59 (2013), https://doi.org/10.1159/000342169.
[101] I.N. Machado, R. Barini, Efeito da corticoterapia pré-natal na evolução de recém-nascidos com enterocolite necrosante Effect of prenatal corticotherapy on the outcome of necrotizing enterocolitis newborns 5, 2007, pp. 252–254.
[102] H. Wiryo, M. Hakimi, A.S. Wahab, P. Soeparto, Association between the absence of colostrum feeding and symptoms of intestinal obstruction or neonatal necrotizing enterocolitis, Paediatr. Indones. 44 (2016), https://doi.org/10.14238/pi44.1.2004.7-11.
[103] J. Olieman, W. Kastelijn, Nutritional feeding strategies in pediatric intestinal failure, Nutrients. 12 (2020) 1–14, https://doi.org/10.3390/nu12010177.
[104] M. Sánchez Luna, S.C. Martin, C.S. Gómez-de-Orgaz, Human milk bank and personalized nutrition in the NICU: a narrative review, Eur. J. Pediatr. 180 (2021), https://doi.org/10.1007/s00431-020-03887-y.
[105] B. Balachandran, S. Dutta, R. Singh, R. Prasad, Praveen Kumar, Bovine colostrum in prevention of necrotizing enterocolitis and sepsis in very low birth weight neonates: a randomized, double-blind, placebo-controlled pilot trial, J. Trop. Pediatr. 63 (2017).
[106] A.M. Ahnfeldt, N. Hyldig, Y. Li, S.S. Kappel, L. Aunsholdt, P.T. Sangild, et al., FortiColos - A multicentre study using bovine colostrum as a fortifier to human milk in very preterm infants: study protocol for a randomised controlled pilot trial, Trials. 20 (2019), https://doi.org/10.1186/s13063-019-3367-7.
[107] E. Bardellini, F. Amadori, A. Majorana, Oral hygiene grade and quality of life in children with chemotherapy-related oral mucositis: a randomized study on the impact of a fluoride toothpaste with salivary enzymes, essential oils, proteins and colostrum extract versus a fluoride toothpaste without menthol, Int. J. Dent. Hyg. 14 (2016), https://doi.org/10.1111/idh.12226.
[108] M. Rathe, S. De Pietri, P.S. Wehner, T.L. Frandsen, K. Grell, K. Schmiegelow, et al., Bovine colostrum against chemotherapy-induced gastrointestinal toxicity in children with acute lymphoblastic leukemia: a randomized, double-blind, placebo-controlled trial, J. Parenter. Enter. Nutr. 44 (2020), https://doi.org/10.1002/jpen.1528.
[109] T. Hisamatsu, T. Kanai, Y. Mikami, K. Yoneno, K. Matsuoka, T. Hibi, Immune aspects of the pathogenesis of inflammatory bowel disease, Pharmacol. Ther. 137 (2013), https://doi.org/10.1016/j.pharmthera.2012.10.008.
[110] M. Sienkiewicz, P. Szymańska, J. Fichna, Supplementation of bovine colostrum in inflammatory bowel disease: benefits and contraindications, Adv. Nutr. 12 (2021) 533–545, https://doi.org/10.1093/advances/nmaa120.
[111] A. Chae, A. Aitchison, A.S. Day, J.I. Keenan, Bovine colostrum demonstrates anti-inflammatory and antibacterial activity in in vitro models of intestinal inflammation and infection, J. Funct. Foods 28 (2017) 293–298, https://doi.org/10.1016/j.jff.2016.11.016.
[112] J. Jin, L. Gramlich, Short bowel syndrome, in: Ref. Modul. Biomed. Sci, 2019, pp. 303–329, https://doi.org/10.1016/B978-0-12-801238-3.65648-9.
[113] V.H. Heemskerk, L.W.E. Van Heurn, P. Farla, W.A. Buurman, F. Piersma, G. Ter Riet, et al., Effect of IGF-rich colostrum on bowel adaptation in neonatal piglets with short bowel syndrome, J. Pediatr. Gastroenterol. Nutr. 34 (2002), https://doi.org/10.1097/00005176-200201000-00011.
[114] P. Lund, P.T. Sangild, L. Aunsholt, B. Hartmann, J.J. Holst, J. Mortensen, et al., Randomised controlled trial of colostrum to improve intestinal function in patients with short bowel syndrome, Eur. J. Clin. Nutr. 66 (2012), https://doi.org/10.1038/ejcn.2012.93.
[115] L. Aunsholt, P.B. Jeppesen, P. Lund, P.T. Sangild, I.B.R. Ifaoui, N. Qvist, et al., Bovine colostrum to children with short bowel syndrome: a randomized, double-blind, crossover pilot study, J. Parenter. Enter. Nutr. 38 (2014), https://doi.org/10.1177/0148607112469630.