NUTRITION REVIEWS

Special Article

Clinical applications of bovine colostrum therapy: a systematic review

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Bovine colostrum, the first milk that cows produce after parturition, contains high levels of growth factors and immunomodulatory components. Some healthy and diseased individuals may gain health benefits by consuming bovine colostrum as a food supplement. This review provides a systematic, critical evaluation of the current state of knowledge in this area. Fifty-one eligible studies were identified from the following databases: Medline, Embase, Global Health, the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature. Studies were heterogeneous with regard to populations, outcomes, and methodological quality, as judged by the Jadad assessment tool. Many studies used surrogate markers to study the effects of bovine colostrum. Studies suggesting clinical benefits of colostrum supplementation were generally of poor methodological quality, and results could not be confirmed by other investigators. Bovine colostrum may provide gastrointestinal and immunological benefits, but further studies are required before recommendations can be made for clinical application. Animal models may help researchers to better understand the mechanisms of bovine colostrum supplementation, the dosage regimens required to obtain clinical benefits, and the optimal methods for testing these effects in humans.

INTRODUCTION

Colostrum is the first milk that mammals produce after parturition, and its composition differs markedly from that of milk produced later in lactation. This fluid has evolved under selective pressure to care for highly sensitive mammalian neonates and is believed to contribute significantly to initial immunological defense in the neonatal period as well as to the growth, development, maturation, and integrity of the neonatal gastrointestinal (GI) tract. Certain effects of colostrum may be species specific, whereas other effects may be shared across species.[1,2] Hence, the unique nutritional and biological activities of bovine colostrum that benefit neonatal calves may also benefit specific groups of humans.

Antimicrobial, immunomodulatory, and growth-stimulating factors in bovine colostrum

Bovine colostrum may have direct antimicrobial and endotoxin-neutralizing effects throughout the alimentary tract as well as other bioactivities that suppress gut inflammation and promote mucosal integrity and tissue repair under various conditions related to tissue injury. Constituents of bovine colostrum may not only have local effects but may also contribute to immunological events, resulting in systemic effects after contact with the gut mucosa. Bovine colostrum contains numerous factors attributable to the acquired and innate immune systems, including a range of peptides and proteins with direct antimicrobial effects.[3]

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In contrast to maternal immunoglobulin in humans, which is transferred across the placenta to the fetus, maternal immunoglobulin in cattle does not cross the placenta. Thus, the newborn calf is dependent on the intestinal absorption of immunoglobulin, which is present in large quantities in bovine colostrum and provides passive immunity after birth.[4] Immunoglobulin concentrations are nearly 100-fold higher in colostrum than in mature milk and are critical for immunological defense in a calf's early days of life.[5]

Components of bovine colostrum attributable to the innate immune system include antimicrobial peptides, such as lactoferrin and lactoperoxidases, which have additive antibacterial effects.[5] Lactoferrin is a glycoprotein with antibacterial as well as antiviral, lipopolysaccharide-binding, and growth-regulating effects. Lactoperoxidase is an antibacterial enzyme that inhibits bacterial metabolism and has been shown to be toxic to a range of gram-positive and gram-negative bacteria; it also possesses antiviral activities. Lysozyme is a lytic enzyme that plays a role in the innate immune system by attacking peptidoglycan cell constituents found primarily in gram-positive bacteria, leading to bacterial lysis.[5]

Bovine colostrum contains a range of immune-regulating and inflammatory cytokines, such as interleukins (IL-1β, IL-2, IL-6, IL-17), tumor necrosis factor-α, interferon-γ, and other nonantimicrobial compounds that contribute to the control of infection and inflammation through cytokine-facilitated crosstalk, pathogen recognition, and immune cell recruitment. In addition, specific microRNA with immune-regulating potential is present in microvesicles, is stable under the degradative conditions of the GI tract, and may have the potential to reach the immune cells of gut-associated lymphoid tissues.[6–8] Bioactive oligosaccharides may be important in protecting against pathogens and promoting the growth of beneficial microflora in the colon.[9]

Bovine colostrum has growth-promoting effects on human intestinal tissue, probably attributable to the combination of several growth factors.[10] The role of luminal growth factors in the healthy adult gut has not been established, as the receptors for many trophic factors are not present luminally. However, these luminal ligands may be able to reach target receptors on the basolateral membranes of mucosal cells in the damaged gut, and detrimental gut conditions may result in the modification of receptor distribution to include apical membranes.[11] Colostrum contains high amounts of the insulin-like growth factors (IGFs) IGF-1 and IGF-2. These hormones are heat and acid stable and are able to withstand dairy processing and the degradative conditions of the GI tract. They facilitate cellular growth, differentiation, and development and may have local effects or be absorbed into the circulation, mediating systemic effects. Bovine colostrum contains vascular endothelial and basic fibroblast growth factors.[12] Platelet-derived growth factor, also present in bovine colostrum, is believed to be an important mitogen for fibroblasts and to serve in wound healing. Transforming growth factor-β, which is present in high concentrations in colostrum, has anti-inflammatory effects, and regulates proliferation, differentiation, and repair in different tissues, is essential in the induction of regulatory T cells. Transforming growth factor-α, on the other hand, is a peptide involved in maintaining epithelial function and integrity.[5,11]

Although many of these compounds are considered labile and may be influenced by different dairy processes, they are present in standardized colostrum derivatives,[12,13] and evidence of the recovery and preserved bioactivity of bovine immunoglobulin after GI transit has been documented.[14,15] However, the effects of more labile components like cytokines may be questionable, and products of different origin, milking times, and formulation may fall under the general term of colostrum.

The aim of this review is to provide a complete evaluation of the current state of knowledge and evidence regarding the effects of enteral supplementation with bovine colostrum. In addition to presenting and discussing previous research, this review highlights remaining challenges and possible future research areas. Other reviews of specific aspects of bovine colostrum supplementation have been published,[11,16–21] but this is the first systematic review providing a comprehensive overview of the field.

METHODS

Search strategy

Electronic literature searches of the Medline PubMed interface, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Global Health databases were conducted using the key words (colostrum OR colostrums) AND (bovine OR cow OR cows OR cattle) as MeSH terms and free text. Searches were limited to human trials published in English from the date of database inception through March 6, 2013. An additional search of Medline records from the previous 6 months (March 6, 2013–September 6, 2012) using identical terms without the human trial limitation was conducted to account for any delay in key word assignment. Bibliographies of the papers identified were scanned to identify additional relevant publications.

Inclusion and exclusion criteria

Following the PRISMA statement,[22] titles and abstracts of identified studies were reviewed using the following

inclusion and exclusion criteria, according to the population, intervention, comparison, and outcome format. Abstracts, single case reports, and letters were not included. Because bovine colostrum may have the capacity to benefit a wide range of the population, all studies of its use as a dietary supplement (food, pill, powder, extract) in healthy and/or diseased humans were considered for inclusion. The use of a control group was not a criterion for inclusion. Studies using a single compound extracted from bovine colostrum were not included. The analysis was restricted to studies of standard or "natural" bovine colostrum preparations and excluded studies of hyperimmune bovine colostrum, which contains large amounts of specific antibodies due to prior immunization of cows with specific microorganisms. Any quantifiable change in a health- or performance-related clinical or paraclinical parameter was accepted as an eligible outcome. Selected reviews and animal and in vitro studies were used as supporting literature.

Quality assessment

The methodological quality of the included studies was evaluated using the three-item Jadad scale,[23] which has been used extensively in clinical research and has shown a high degree of inter-rater reliability.[24,25] It is used to evaluate three domains of study quality: randomization, blinding, and withdrawals/dropouts. Scores range from 0 to 5, with higher scores indicating better quality (≥3 = methodologically sound). Studies that did not employ a comparative methodology, such as those evaluating the effect of an intervention without a control group or crossover design, were given a default score of 0. The 2011 impact factor (in Journal Citation Reports) of the journal in which each study was published was recorded, if available.

RESULTS

Literature search

The initial literature search identified 1,366 publications (Embase, $n = 427$; CINAHL, $n = 32$; Global Health, $n = 359$; Cochrane Library, $n = 60$; Medline, $n = 488$). Four additional papers were identified through other sources. After the removal of duplicates ($n = 581$), 789 papers remained eligible for screening. Screening identified 49 papers that reported on 51 studies of the effect of bovine colostrum supplementation that met the eligibility criteria. Figure 1 is a flowchart of the study selection process.

Trial characteristics

The 51 studies included in the analysis were conducted in Europe ($n = 24$, 47%), the United States ($n = 8$, 16%), Asia ($n = 4$, 8%), Australia or New Zealand ($n = 13$, 25%), and Africa ($n = 2$, 4%). A total of 2,326 patients (range, 3–605 patients/trial; mean, $n = 47.5$; median, $n = 29$) were collectively enrolled. Table 1 provides an overview of the included studies. Briefly, the analysis identified the following trial types: two double-blind, crossover, randomized trials (RTs) of nonsteroidal anti-inflammatory drug (NSAID)-induced GI toxicity, reported in one article[26]; five trials examining HIV-associated diarrhea and immunosuppression, including one case series,[27] three open-label, uncontrolled, observational studies,[28–30] and one open-label, uncontrolled, randomized study[31]; two placebo-controlled RTs investigating the effects of bovine colostrum supplementation on inflammatory responses and microbial translocation after surgery[32,33]; two double-blind, placebo-controlled, crossover RTs investigating the effects of bovine colostrum supplementation on intestinal function and adaptation in short bowel syndrome (SBS)[34,35]; one observational study of the effects of bovine colostrum supplementation in patients with type II diabetes[36]; seven trials concerning the prevention and/or treatment of upper respiratory tract infection (URTI) or gastroenteritis[37–42]; four trials concerning the modulation of innate or adaptive immunological responses[43–46]; one single-blind, uncontrolled RT evaluating the effect of bovine colostrum in infants and children with nonorganic failure to thrive[47]; two RTs evaluating the effects of bovine colostrum on irritable bowel syndrome[48] and juvenile idiopathic arthritis[49]; a case series evaluating the effect of bovine colostrum in chronic pain syndrome[50]; and 24 trials investigating athletic performance, body composition, nutrient absorption, and endocrinological or immune functions during exercise in healthy subjects.[51–74]

Methodological quality

Jadad scale scores ranged from 0 to 5 (mean, 2.8). Sixteen trials (31%) were of poor methodological quality (score ≤2). Only two trials obtained maximum scores. The median journal impact factor for the included studies was 2.48 (range, 0.521–5.43). Impact factor was not associated with the assigned methodological ratings.

Ineligible studies

The literature search identified several studies that were not eligible for inclusion in this review, including two trials that used lactoferrin from bovine colostrum[75,76]; one study investigating the use of a colostrum-containing mouth hygiene product in Sjögren's syndrome and oral lichen planus[77]; one study investigating the effect of colostrum-containing eye drops for the treatment of eye dryness[78]; one study investigating the effect of topical

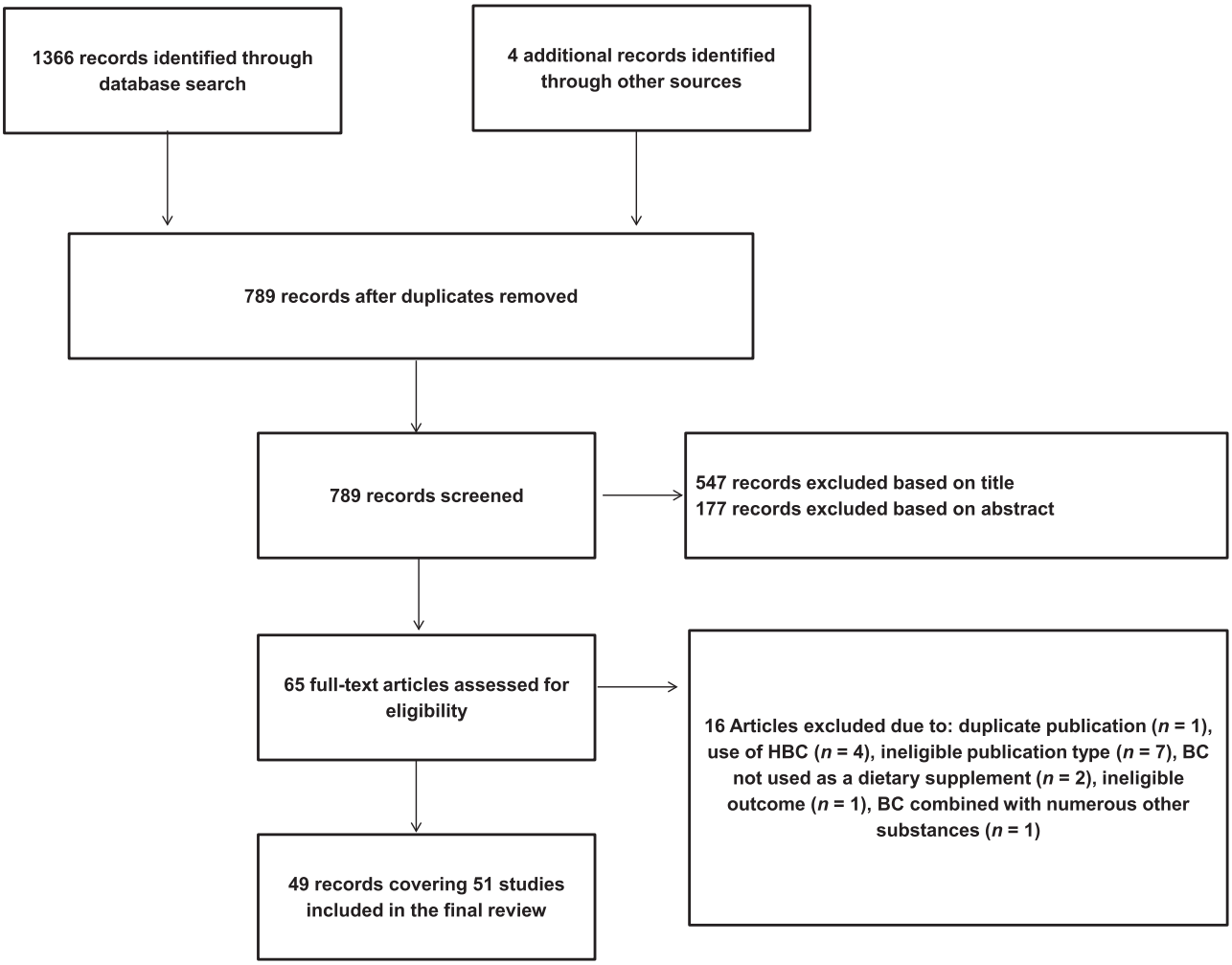

Figure 1 Flowchart of the study selection process.
Abbreviations: BC, bovine colostrum; HBC, hyperimmune bovine colostrum.

colostrum on dental plaque[79]; and two studies of inflammatory bowel disease, comprising one double-blind, placebo-controlled RT of colostrum enemas[80] and one small case study investigating the use of a dietary supplement containing a range of different substances that included, among others, bovine colostrum. In this last study, however, it would be impossible to attribute an effect to bovine colostrum.[81]

DISCUSSION AND SUMMARY OF STUDIES

NSAID- and surgery-induced gut damage

NSAIDs are widely prescribed due to their analgesic, anti-inflammatory, and antipyretic effects. Their use, however, may have severe adverse effects, such as gastric ulceration and injury to the small and large intestines. The results of in vitro, animal, and human studies have suggested that bovine colostrum supplementation protects against the adverse effects of these drugs in the gut.[26,82–85] Playford et al.[82] found that bovine colostrum supplementation resulted in a dose-dependent reduction in gastric injury after indomethacin administration in a rat model and prevented villus shortening in a mouse model of indomethacin-induced small intestinal injury. Other authors found that bovine colostrum alone or in combination with glutamine reduced NSAID-induced declines in serum total protein and albumin levels as well as the NSAID-induced increase in intestinal permeability, resulting in reduced bacterial overgrowth and less bacterial translocation to the mesenteric lymph nodes, liver, spleen, and peripheral blood.[83,86] Bovine colostrum has also effectively reduced bacterial translocation in rats with carrageenan-induced intraperitoneal inflammation.[87]

Table 1 **Overview of the studies included in the review.**

Reference	Population	No. of subjects (M/F)	Study design	Exposure or condition	Dosage and duration	Endpoints	Jadad score	Outcomes
NSAID- and surgery-induced gut damage								
Playford et al. (2001)[26]	Healthy volunteers	7 (7/0)	R; DB; PC; CRO	Indometacin 50 mg t.i.d.	125 mL t.i.d. for 7 days	Intestinal permeability	4	↓Intestinal permeability
Playford et al. (2001)[26]	NSAID users	15 (7/8); 14 finished	R; DB; PC; CRO	NSAID use for ≥1 year	125 mL t.i.d. for 7 days	Intestinal permeability	4	No significant effect
Bolke et al. (2002)[32]	Coronary bypass patients	60 (54/6)	R; PC; level of blinding NS	Coronary bypass	42 g 2 days preoperatively	Endotoxin; ENC; CRP; IL-6	3	No significant effect
Bolke et al. (2002)[33]	Abdominal surgery patients	40 (22/18)	R; PC; level of blinding NS	Abdominal surgery	56 g 3 days preoperatively	Endotoxin; ENC; CRP; IL-6	2	↓Endotoxin; ↑ENC
HIV-associated diarrhea and immunosuppression								
Saxon & Weinstein (1987)[27]	2 AIDS patients, 1 other	3 (3/0)	Case series	*Cryptosporidium*	1, 3, or 5 L for 5–7 days	Diarrhea	0	No significant effect
Rump et al. (1992)[28]	27 adult HIV patients, 2 pediatric HIV patients, 8 others	37 (31/6)	OBS; UC	Diarrhea (>4 stools/day) for >2 weeks	10 g daily for 10 days	Stool frequency; body weight	0	↓Stool frequency; body weight stable
Plettenberg et al. (1993)[29]	HIV-positive adults	25 (25/0)	OBS; UC	Diarrhea (≥3 stools/day) for ≥1 month	10 g daily for 10 days	Stool frequency	0	↓Stool frequency
Flóren et al. (2006)[30]	HIV-positive adults	30 (15/15)	OBS; UC	Diarrhea (≥4 stools/day) for ≥5 days	16 g b.i.d. for 4 weeks	Stool frequency; self-reported fatigue; $CD4^+$ count; body weight	0	↓Stool frequency;↓ fatigue;↑CD4+ count; ↑body weight
Kaducu et al. (2011)[31]	HIV-positive adults not receiving ARV	87 (27/60)	R; open	Diarrhea (≥4 stools/day) for ≥7 days	16 g b.i.d. for 4 weeks	Stool frequency; self-reported fatigue; $CD4^+$ count; body weight	3	↓Stool frequency;↓fatigue; ↑$CD4^+$ count;↑body weight
Sports nutrition and exercise								
Antonio et al. (2001)[51]	Recreational athletes	22 (14/8); 21 finished	DB; PC	Maintain habitual level of exercise	20 g daily for 8 weeks	1-RM; maximum repetitions; TTE; LBM	2	↑LBM
Coombes et al. (2002)[54]	Competitive cyclists	42 (42/0); 28 finished	R; DB; PC	Habitual level of exercise	20 or 60 g daily for 8 weeks	VO_{2max} test; time trial; IGF-1; body composition	3	↑Time trial results
Buckley et al. (2002)[56]	Recreational athletes	30 (30/0)	R; DB; PC	Three 45-min runs/week	60 g for 8 weeks	Peak running speed in 2 consecutive runs; IGF-1	3	↑Peak running speed in 2nd run
Hofman et al. (2002)[74]	Elite field hockey players	35 (18/17); 28 finished	R; DB; PC	Habitual level of exercise	60 g for 8 weeks	Sprint test; suicide test; shuttle run; vertical jump; anthropometrics	3	↑Sprint test performance
Brinkworth et al. (2002)[59]	Elite rowers	13 (0/13)	R; DB; PC	Rowing and strength-plyometric training	60 g for 9 weeks	Mechanical work in 2 consecutive rows; body composition; blood buffering	4	↑Blood buffering capacity
Kuipers et al. (2002)[73]	Endurance athletes	9 (9/0)	OBS; UC	Tested before and after	60 g for 4 weeks	IGF-1; IGF-BP3; urine drug test	0	No significant effect
Fry et al. (2003)[62]	Recreational athletes	19 (13/6)	R; DB; PC	Heavy-resistance exercise 4 days/week	60 g for 12 weeks (4 groups)	1-RM; fiber type percentage; fiber type area; myosin heavy chain; body composition	3	No significant effect
Buckley et al. (2003)[57]	Recreational athletes	51 (51/0)	R; DB; PC	Resistance training 3×/week, nonresistance exercises	60 g daily for 8 weeks	Vertical jump;, cycling power; alactic work capacity; 1-RM; IGF-1	4	↑Vertical jump; ↑cycling power
Brinkworth & Buckley (2003)[60]	Healthy males	12 (12/0)	R; DB; PC	OGTT; OATT	60 g for 8 weeks	OGTT; OATT	4	No significant effect
Brinkworth & Buckley (2004)[61]	Elite rowers	13 (0/13)[a]	R; DB; PC	Rowing and strength-plyometric training	60 g for 9 weeks	Plasma buffering capacity	4	No significant effect

Table 1 **Continued**

Reference	Population	No. of subjects (M/F)	Study design	Exposure or condition	Dosage and duration	Endpoints	Jadad score	Outcomes
Brinkworth et al. (2004)[58]	Recreational athletes	34 (34/0)	R; DB; PC	4 days/week, resistance training of elbow flexors in nondominant arm	60 g for 8 weeks	Limb circumference; limb CSA; maximum voluntary isometric strength; 1-RM	4	↑Limb circumference; ↑limb CSA
Mero et al. (2005)[63]	Recreational athletes	12 (12/0)	R; DB; PC; CRO	Heavy strength training session	20 g for 2 weeks	IGF-1; strength performance; S-amino acids; protein balance; muscle biopsy	4	↑S-essential amino acids; ↑protein synthesis and breakdown
Shing et al. (2006)[53]	Highly trained cyclists	29 (29/0)	R; DB; PC	Habitual level of exercise and 5 days of HIT	10 g for 8 weeks and 1 day	40-km time trial; VO_{2max} test; TTE	3	Improved 40-km time trial after HIT; ↑ventilatory threshold
Kerksick et al. (2007)[66]	Recreational athletes	49 (36/13)	R; DB; PC	Total-body resistance training	60 g for 12 weeks (4 groups)	FFM; 1-RM and 80% of 1-RM; 30-sec sprint tests	4	↑FFM
Immune functions in sport and exercise								
Mero et al. (1997)[64]	Recreational athletes	9 (9/0)	R; DB; PC; CRO	8 days strength and speed training; 13 days washout	125 or 25 mL for 8 days	IGF-1; IgA; IgG; countermovement jump; hormones; amino acids	3	↑IGF-1 for 125 mL
Mero et al. (2002)[65]	Recreational athletes	30 (16/14)	R; DB; PC	Habitual level of exercise	20 g for 2 weeks	IGF-1; IgA; IgG	4	↑IGF-1; ↑secretory IgA
Crooks et al. (2006)[69]	Recreational distance runners	39 (22/17); 35 analyzed	R; DB; PC	Habitual level of exercise	26 g (10 g colostrum) for 12 weeks	Salivary IgA; self-reported URTS	4	↑Salivary IgA
Shing et al. (2007)[52]	Elite cyclists	29 (29/0)	R; DB; PC	Habitual level of exercise and 5 days of HIT	10 g for 8 weeks and 1 day	NK cell toxicity; salivary IgA; cytokines; IgG; CRP; lymphocyte and neutrophil surface markers; URTS	4	↑IgG2; ↑sTNF-1; ↑cytotoxic T cells
Buckley et al. (2009)[55]	Recreational athletes	30 (30/0)	R; DB; PC	Running at lactate threshold 3 days/week	60 g for 8 weeks	Intestinal permeability; body mass; peak oxygen uptake; TTE; heart rate	3	↑Intestinal permeability
Davison & Diment (2010)[68]	Recreational athletes	20 (20/0)	R; DB; PC	2 h of exercise at 64% VO_{2max}	20 g for 28 days	In vitro neutrophil degranulation; salivary IgA; lysozyme; blood lactate; blood glucose; P-cortisol	3	↑Speed of neutrophil degranulation; ↑lysozyme concentration and secretion
Crooks et al. (2010)[70]	Elite swimmers, nonexercising controls	25 (12/13); 28 (9/10)	R; DB; PC	12 weeks swim training	50 g for 10 weeks corresponding to 20 g of colostrum	Saliva and blood IgA; IgM; IgG; URTS	4	No significant effect
Marchbank et al. (2011)[67]	Recreational athletes	12 (12/0)	DB; PC; CRO	20-min run at 80% VO_{2max}	20 g for 14 days	Gut hormones; intestinal permeability	2	↓Intestinal permeability; ↓GLP-1
Carol et al. (2011)[71]	Well-trained athletes	10 (10/0); 9 analyzed	R; DB; PC; CRO	Glycogen depletion trial; endurance trial	25 g for 10 days	Plasma glucose; lactate; serum cortisol; cell counts; Ig; CRP and cytokines	4	No significant effect
Appukutty et al. (2011)[72]	Adolescent athletes	40 (40/0)	R; DB; PC	Habitual level of exercise	20 g daily for 6 weeks	In vitro IFN-γ	4	↓In vitro IFN-γ
Infection and immune responses								
McClead et al. (1988)[37]	Males >16 years with *V. cholera* diarrhea	45 (45/0)	R; PC	BC, HBC, or water	2 g twice	Stool volume; stool IgG and IgA; toxin-neutralizing activity	1	No effect on stool volume; ↑stool IgG; ↑stool IgA
McClead et al. (1988)[37]	Males >16 years with *V. cholera* diarrhea	20 (20/0)	R; PC	BC, HBC, or water	2 g × 8	Stool volume; stool IgG and IgA; toxin-neutralizing activity	1	No effect on stool volume; ↑stool IgG; ↑stool IgA
Huppertz et al. (1999)[42]	Children with diarrheagenic *E. coli*	27 (13/14)	R; DB; PC	Infection with diarrheagenic *E. coli*	21 g for 14 days	Stool frequency; elimination of strains expressing virulence factors	4	↓Stool frequency
He et al. (2001)[44]	Healthy adult volunteers	18 (9/9)	R; PC; level of blinding NS	Oral vaccine against *S. typhi* Ty21a	100 mL for 7 days	Antibody-secreting cells; CR6 IgG receptors	2	No significant effect
Brinkworth & Buckley (2003)[38]	Healthy volunteers	174 (174/0)	R; DB; PC[b]	Participants in earlier trials	60 g for 8 weeks	Self-reported URTS	4	↓Self-reported URTS
Patel & Rana (2006)[39]	Patients aged 1–8 years	605 (341/210); 551 finished	Open; UC	Recurrent URTI or diarrhea	3 g for 12 weeks	Self-reported URTS; diarrhea; hospitalization	0	↓Self-reported URTS; ↓diarrhea; ↓hospitalization

Lindbaek et al. (2006)[40]	Male soldiers	NS	R; DB; PC	Nonstreptococcal sore throat	NS	Illness duration	2	No significant effect
Wolvers et al. (2006)[45]	Healthy adult volunteers	138 (42/89); 131 finished	R; DB; PC	Tetanus toxoid vaccine; typhoid vaccine	1.2 g daily	DTH; leukocyte subsets; phagocytosis; oxidative burst; lymphocyte proliferation	3	No significant effect
Patiroglu & Kondolot (2013)[41]	Children with IgA deficiency	31 (18/13)	R; DB; PC	Clinically established URTI	14 mg t.i.d. for 1 week	Self-reported severity score; URTS duration; salivary IgA	5	↓Self-reported severity score
Mikic et al. (2012)[43]	Healthy adult volunteers	20 (6/14)	R; no placebo		480 mg b.i.d. for 30 days	Salivary IgA	3	↓Salivary IgA
Jensen et al. (2012)[46]	Healthy adult volunteers	12 (6/6)	R; DB; PC; CRO		150 mg once	Phagocytic activity; leukocyte counts and subsets; T and NK cell counts	4	↑Phagocytic activity; ↓NK cells
Short bowel syndrome								
Lund et al. (2012)[34]	Adult patients with SBS	12 (7/5); 8 analyzed	R; DB; PC; CRO	SBS in clinically stable phase	500 mL daily	Grip strength; lung function; body composition; intestinal function	3	No significant effect
Aunsholt et al. (2014)[35]	Children with SBS	9 (5/4)	R; DB; PC; CRO	SBS in clinically stable phase	20% enteral intake for 4 weeks	Intestinal energy absorption; wet weight; growth; IGF-1; IGF-BP3	5	No significant effect
Growth and metabolic disorders								
Kim et al. (2009)[36]	Adults with type 2 diabetes	18 (9/9)	OBS; UC	Type 2 diabetes	10 g daily	Postprandial blood glucose; triglycerides; cholesterol; ketone bodies	0	↓Postprandial blood glucose; ↓triglycerides; ↓cholesterol; ↓ketone bodies
Panahi et al. (2010)[47]	Children with failure to thrive	120 (71/49)	R; SB; UC	Nonorganic failure to thrive	40 mg/kg/day	Gomez and Waterlow indices	2	↑Gomez index of growth insufficiency
Juvenile idiopathic arthritis								
Malin et al. (1997)[49]	Children with JIA	30 (13/17)	R; C; DB	JCA	10 g	TNF-α; ISC; sACS fecal enzymes; TNF-α and α-1-antitrypsin	4	↑Fecal urease
Chronic pain syndrome and irritable bowel syndrome								
Ragab et al. (2007)[48]	Adults with IBS	110 (85/25)[c]	R; PC; DB	Adults with IBS	10 mL daily for 2 weeks, followed by 20 mL daily for 10 weeks	IBS symptoms	4	No effect at end of treatment
Waaga-Gasser et al. (2009)[50]	Adults with CPS	4 (2/2)	Case series	CPS with good response to BC therapy	20 g–1 g daily	Flow cytometry; cytokine analysis; IGF-1; apoptosis	0	Apoptotic effect on monocytes

Abbreviations and symbols: ↓, decrease; ↑, increase; 1-RM, one-repetition maximum; ARV, anti-retroviral therapy; BC, bovine colostrum; C, controlled; CPS, chronic pain syndrome; CR, complement receptor; CRO, crossover; CRP, C-reactive protein; CSA, cross-sectional area; DB, double-blind; DTH, delayed-type hypersensitivity; ENC, endotoxin-neutralizing capacity; F, female; FFM, fat-free mass; GLP-1, glucagon-like peptide 1; HBC, hyper-immune bovine colostrum; HIT, high-intensity training; IBS, irritable bowel syndrome; IFN-γ, interferon gamma; Ig, immunoglobulin; IGF-1, insulin-like growth factor 1; IGF-BP3, insulin-like growth factor binding protein 3; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; ISC, immunoglobulin-secreting cells; JIA, juvenile idiopathic arthritis; JCA, juvenile chronic arthritis; LBM, lean body mass; M, male; NK, natural killer; NS, not stated; NSAID, non-steroidal anti-inflammatory drug; OATT, oral L-alanine tolerance test; OBS, observational; OGTT, oral D-glucose tolerance test; PC, placebo-controlled; R, randomized; sACS, specific antibody-secreting cells; SB, single-blind; SBS, short bowel syndrome; sTNF-1, soluble tumor necrosis factor 1; TNF-α, tumor necrosis factor α; TTE, time to exhaustion; UC, uncontrolled; URTI, upper respiratory tract infection; URTS, upper respiratory tract symptoms; VO_{2max}, maximal oxygen uptake.

[a] Data collected in previous study.[59]

[b] Pooled retrospective data from earlier trials.

[c] Contradiction between text and table.

Although the mechanisms of such beneficial effects of bovine colostrum remain undetermined, the presence of growth factors is thought to contribute to the maintenance of equilibrium of mucosal mass and integrity in the GI tract.[11] This proposal is supported by in vitro evidence that bovine colostrum increases proliferation and migration of human colonic carcinoma cells and rat intestinal cells, suggesting that it has the ability to stimulate growth and repair in the GI tract.[82] Furthermore, the C-terminal half of the colostrum protein lactoferrin has the ability to sequester unbound NSAIDs in the GI tract and may thus protect against NSAID-induced gastropathy.[85] A mouse model of C-lobe and NSAID coadministration showed significant reduction of gastric bleeding and inflammation.[84]

Despite the promising results in animal models, few human trials on this topic have been undertaken. Playford et al.[26] conducted two crossover RTs evaluating the effects of bovine colostrum on NSAID-induced intestinal damage. In the first study, 7 healthy male volunteers received colostrum (125 mL, 3 times per day for 7 days) or an isoproteinaceous milk whey protein solution. Following microfiltration (0.2 µm pore), the colostrum (Bioenervi; Viable Bioproducts, Turku, Finland) was free of fat and lactose and reduced in major proteins such as casein and lactalbumin, with the remaining protein being relatively rich in immunoglobulin and growth factors. Subjects also received indomethacin (50 mg, 3 times per day) for the last 5 days. Intestinal permeability was assessed at baseline and after 7 days. Bovine colostrum supplementation significantly reduced the NSAID-induced increase in intestinal permeability. In the second study, 15 patients who had taken nonselective NSAIDs for at least 1 year received 125 mL of the same colostrum preparation or a milk whey protein solution 3 times per day for 7 days, with a 2-week washout period between study arms. Bovine colostrum supplementation had no significant direct effect on gut permeability, but baseline gut permeability in patients taking NSAIDs was similar to or lower than that in control subjects not receiving NSAIDs.[26] These studies provided evidence that bovine colostrum or a derivative thereof may protect the GI tract from NSAID-induced injury. However, further clinical studies of sufficient power evaluating outcomes in patients who have taken NSAIDs for longer periods of time are warranted.

Two placebo-controlled RTs investigating the effects of bovine colostrum supplementation on inflammatory responses and microbial translocation after surgery were included in this review.[32,33] Both studies used Lactobin (Biotest Pharma, Dreieich, Germany), a spray-dried immunoglobulin-enriched powder.[88] The placebo product was an identical mix of formula and raspberry flavor without the colostrum preparation. The first study[33] included 40 patients undergoing intra-abdominal surgery who received the immunoglobulin-enriched colostrum preparation (56 g) or placebo for 3 days preoperatively. Endpoints included serial evaluation of endotoxin levels during the first 7 days postsurgery. Compared with patients receiving placebo, those receiving the colostrum preparation had significantly lower endotoxin levels, indicating that the loss of endotoxin-neutralizing capacity was reduced.[33] In a similar study,[32] 60 patients undergoing coronary bypass surgery were randomized to receive the colostrum preparation (42 g for 2 days) or placebo. Colostrum supplementation did not reduce the amount of endotoxin in the bloodstream or shorten the duration of postoperative endotoxemia.[32] Notable differences in the designs of these studies, other than the type of surgery, were the colostrum dose and the duration of supplementation. Neither study found any effect of colostrum supplementation on the clinical course of patients.

Available evidence suggests that bovine colostrum supplementation may reduce microbial translocation across the gut mucosa in patients undergoing abdominal surgery. Such an effect may be attributable to direct antimicrobial and endotoxin-neutralizing effects as well as to the suppression of gut inflammation and the promotion of mucosal integrity and tissue repair.

HIV-associated diarrhea and immunosuppression

Diarrhea is a common complication of HIV infection, with a multifactorial etiology that may include common pathogens, opportunistic agents, or noninfectious factors. HIV infection may lead to the loss of gut-mucosal $CD4^+$ cells, thereby compromising the epithelial barrier function of the gut mucosa and enabling microbial translocation, resulting in GI and systemic immune activation. Thus, HIV-associated diarrhea may not only result in discomfort and malnutrition but may also affect the immunological and inflammatory status of patients.[16,89]

This review includes five studies of the role of bovine colostrum in HIV-associated diarrhea.[27–31] Although the studies are generally of poor methodological quality (Table 1), they collectively suggest a positive effect of bovine colostrum supplementation. In an open, uncontrolled, observational study, Rump et al.[28] administered 10 g of bovine colostrum concentrated for immunoglobulin to 27 adults and 2 children with HIV infection. The colostrum product was a casein-precipitated, fat-free, spray-dried powder.[88] This treatment led to transient or long-lasting normalization of stool frequency in the majority of patients. Plettenberg et al.[29] performed an open, uncontrolled study in 25 HIV-infected patients with chronic diarrhea with no demonstrable pathogen ($n = 18$) or cryptosporidiosis ($n = 7$). Ten days

of supplementation with 10 g of bovine colostrum (Lactobin)[88] led to complete remission in 40% (10/25) of patients.

In an open-label observational study, Florén et al.[30] investigated the effect of a porridge containing 32% bovine colostrum powder (ColoPlus; ColoPlus AB, Malmö, Sweden). Consumption of this preparation reduced HIV-associated diarrhea, with a significant decrease in the daily number of bowel evacuations. Fatigue decreased by 81% during the study period. Furthermore, patients showed concomitant increases in hemoglobin and albumin concentrations, $CD4^+$ counts, and body weight. These findings were confirmed in a 2011 open-label RT involving 87 adult patients with HIV who were not receiving antiretroviral therapy. The patients were randomized to colostrum supplementation for 28 days (porridge containing 32% bovine colostrum powder, ColoPlus) or standard care. Patients receiving supplementation showed a significant reduction in diarrhea, with a decrease in daily stool frequency from 7.3 to 1.3, and an 85% decrease in self-reported fatigue, which was significantly greater than that reported by controls. $CD4^+$ counts increased by 14% and body weight increased by 11% in colostrum-treated patients.[31] Because these studies used porridges containing 32% bovine colostrum and no placebo, improved nutritional status may have contributed significantly to the observed effects.[30,31] Current evidence, however, suggests that bovine colostrum can effectively ameliorate HIV-associated diarrhea, possibly due to direct antimicrobial and endotoxin-neutralizing effects and the suppression of gut inflammation as well as to the promotion of mucosal integrity and tissue repair. These findings must be confirmed in future placebo-controlled RTs.

Sports nutrition and exercise

The effect of bovine colostrum supplementation on athletic performance has received considerable attention, primarily based on the hypothesis that bovine colostrum may improve nutrient absorption and body composition. The high levels of growth factors known to stimulate protein synthesis, in addition to early findings that bovine colostrum supplementation increased IGF-1 concentrations in male sprinters,[64] have prompted interest in the possible effects of bovine colostrum on body composition, muscle strength, and endurance in active individuals.

This review includes studies conducted with competitive-level[53,54,59,74] and recreational[51,57,58,62,63,66] athletes. Several studies found that bovine colostrum had positive effects on various aspects of athletic performance,[53,54,56,57,74] whereas others were not able to confirm these findings.[51,58,59,61–64,66,73] The majority of the studies used the same standardized, low-heat, low-fat, low-lactose, concentrated bovine colostrum powder (Intact; Numico Research Australia Pty Ltd, Adelaide, Australia) and a whey-protein-based control supplement.[53,54,56–62,73,74] Mero et al.[63] used a freeze-dried colostrum product (Dynamic colostrum; Hi-Col, Oulu, Finland) and a maltodextrin placebo, while Antonio et al.[51] used powdered whole colostrum (Symbiotics, Sedona, AZ, USA) and a whey protein concentrate placebo. Kerksick et al.[66] used a colostrum powder not further specified and an isocaloric and isonitrogenous blend of whey and casein placebo in addition to creatine.

In a placebo-controlled RT conducted in 29 male elite cyclists, Shing et al.[53] found that supplementation with 10 g of colostrum daily improved cycling performance after 5 days of high-intensity training while reducing the decrease in the ventilatory threshold. Similarly, a double-blind placebo-controlled trial in 35 elite field hockey players randomized to receive 60 g of bovine colostrum daily or whey protein concentrate for 8 weeks showed that colostrum improved sprint performance and significantly reduced sprint times compared with the whey protein group.[74] Buckley et al.[57] found that supplementation with 60 g of bovine colostrum daily had significant beneficial effects on peak cycling and vertical jumping powers after 8 weeks, but not after 4 weeks, suggesting that the duration of supplementation may be important.

The findings of animal studies have suggested that the effect of bovine colostrum on athletic performance is related to better recovery after exercise.[90] In humans, Buckley et al.[56] tested peak speed in two consecutive runs separated by a 20-min recovery period. Colostrum supplementation (60 g daily) for 8 weeks did not improve performance in the first run but significantly increased peak speeds in the second run. These findings were supported in a study of 28 male competitive cyclists.[54] Eight weeks of bovine colostrum supplementation (20 g or 60 g) significantly improved the amount of work completed in a second bout of exercise after 2 hours of cycling at 65% maximal oxygen uptake compared with placebo, but no significant difference between doses was detected. These results suggest an improved ability to recover after exercise, independent of colostrum dosage.[54]

Some studies have found that colostrum affects body composition,[51,58,66] whereas others have not.[54,59,62,74] The IGF-1 in bovine colostrum is structurally identical to that in humans,[91] and an increase in the serum IGF-1 level induced by bovine colostrum supplementation may have positive effects on protein synthesis and body composition. Some authors have found that bovine colostrum supplementation increases serum IGF-1 levels,[64,65] whereas others have been unable to confirm these findings.[35,54,56,57,73] Similarly, the effect on nutrient absorption

capacity demonstrated by some authors[63] has not been confirmed by others.[60,64] No impact of bovine colostrum supplementation has been found on plasma cortisol, growth hormone, or testosterone level.[64,68,71]

In a randomized controlled trial,[66] 49 healthy subjects received supplements of 60 g of colostrum, casein/whey, creatine, or combinations thereof. The two combinations of whey/casein protein plus creatine and colostrum plus creatine both led to greater increases in fat-free mass. This result, however, may have been due to the addition of creatine. Thus, no conclusion regarding the effect of colostrum can be drawn from this study.[66] A double-blind, placebo-controlled trial in 22 recreational athletes supplemented with 20 g of colostrum for 8 weeks documented significantly increased lean body mass as measured by dual-energy X-ray absorptiometry, leading the authors to suggest that colostrum supplementation had an anabolic effect.[51] This proposal was supported by the findings that supplementation with 60 g daily for 8 weeks during resistance training increased limb circumference and cross-sectional area compared with placebo[58] and that 2 weeks of supplementation with 20 g of colostrum increased serum levels of essential amino acids.[63] In a study of 12 healthy adult males, however, 8 weeks of colostrum supplementation had no effect on intestinal nutrient absorption.[60] Thus, while evidence supports continuous research on the effects of bovine colostrum on sports performance, body composition, and nutrient absorption, these data are not unequivocal. Studies in this area have generally been of acceptable methodological quality but are often limited by a small number of participants. Moreover, studies have used heterogeneous endpoints, producing contradictory results, many of which remain unconfirmed.

Immune function in sport and exercise

Strenuous exercise may cause immunosuppression that affects the innate and adaptive immune systems, increasing athletes' susceptibility to infection, particularly URTI. While prolonged intense exercise may increase the risk of infection, moderate exercise, on the other hand, may improve the ability to resist URTI, illustrating the complexities of these mechanisms.[92] Although the relationship between exercise and URTI is poorly understood and may depend on several individual determinants, the identification of several immune-activating and antimicrobial factors in colostrum has led to the hypothesis that colostrum intake may support or stimulate immune functions in athletes.[19]

Several studies have investigated the potential of bovine colostrum supplementation to prevent postexercise immune suppression.[38,52,55,64,65,67–72] Mucosal defenses and levels of secretory immunoglobulin (Ig) A (IgA) have received particular attention, although numerous other immune variables have been investigated.

In a double-blind RT, Shing et al.[52] found that, compared with a whey-protein-based control supplement, 10 g of colostrum (Intact) per day prevented postexercise reduction in IgG2 levels and cytotoxic/suppressor $CD3^+CD8^+$ T cells in 29 male cyclists. These effects were demonstrated after a period of prolonged stress-inducing exercise. In contrast, Carol et al.[71] compared 25 g of skimmed freeze-dried colostrum and a skimmed milk placebo and found no effect of colostrum on measured immune variables after short-term intense exercise in 10 healthy male athletes.

Secretory IgA is known to serve as the first line of defense in protecting mucosal surfaces from enteric toxins and pathogenic microorganisms, thereby playing a key role in the protection of the respiratory, GI, and genitourinary tracts.[93]

In a study of 20 healthy subjects, Davison and Diment[68] found increased stimulated neutrophil degranulation speed in vitro 1 hour after exercise and reduced exercise-induced alterations in lysozyme concentration and secretion in subjects who received a bovine colostrum powder supplement (Neovite, London, UK) versus an isocaloric isomacronutrient mix of milk protein concentrate and skimmed milk powder. In agreement with the findings of other studies, these authors found no effect on IgA concentration.[64,70] Other authors, however, have documented significantly increased salivary IgA levels after bovine colostrum supplementation.[65,69] Mero et al.[65] reported a 33% increase in salivary IgA levels in healthy athletes after 2 weeks of daily supplementation with 20 g of freeze-dried colostrum (Dynamic colostrum) versus a maltodextrin placebo. This finding was supported by the study of Crooks et al.,[69] who found that 12 weeks of bovine colostrum supplementation (Immunolac; NZMP Ltd, Auckland, New Zealand) significantly increased salivary IgA levels compared with a skimmed milk placebo in 39 long-distance runners. In a subsequent study of 25 elite swimmers and 28 students randomly assigned to receive bovine colostrum or placebo, however, Crooks et al.[70] found that a low-protein colostrum powder had no effect on salivary immunoglobulin levels compared with an isocaloric placebo of skimmed milk powder and milk protein concentrate.

Another aspect of comprised immunity in athletes is the exercise-induced increase in gut permeability. In a placebo-controlled crossover RT in 12 healthy male subjects, bovine colostrum powder reduced the exercise-induced increase in intestinal permeability compared with an isoenergetic isomacronutrient mix of milk protein concentrate and skimmed milk powder. In vitro investigations suggested that this effect was due to reduced temperature-induced apoptosis in HT29 cells

and enhanced induction of heat-shock protein.[67] Of further interest, bovine colostrum was shown to significantly reduce heat-induced gut hyperpermeability in a rat model. In rats whose core body temperature was raised, significantly less 51Cr-EDTA transferred into the bloodstream of colostrum-fed rats compared with rats fed a control diet.[94] Another study in 30 healthy male subjects[55] found increased intestinal permeability in those who consumed 60 g of bovine colostrum daily (Intact) compared with those who received a whey-protein-based control supplement. There was, however, no increase in intestinal permeability due to the exercise protocol; thus, these results are inconclusive with respect to the effects of exercise on gut permeability.

Exercise-induced immune depression is of multifactorial origin. Prolonged intense training may have measurable effects on leukocyte counts, oxidative burst activity, natural killer cell activity, mucosal immunoglobulin levels, and proinflammatory cytokine release, but no correlation between these surrogate markers and immunocompetence has been established and thus the effect of a change in one or more parameters with regard to in vivo immune capability is unclear. Overall, exercise studies have not provided conclusive evidence for the effects of colostrum on immunity, but observations of humoral immunity are of potential interest and deserve further investigation and confirmation.

Infection and immune responses

This review included nine articles reporting on 7 adult[37,38,40,52,69,70] and 3 pediatric[39,41,42] studies of the treatment and prevention of URTI and diarrhea. In a double-blind, placebo-controlled RT, Brinkworth and Buckley[38] retrospectively pooled data from several previous studies examining self-reported URTI symptoms in 174 healthy adult males receiving bovine colostrum (Intact) or a whey-protein-based control supplement. Significantly fewer subjects receiving bovine colostrum reported URTI symptoms within 7 weeks after discontinuation of the intervention compared with those receiving placebo. Bovine colostrum had no effect on symptoms once they had developed.[38] Shing et al.[52] reported a trend toward a reduced incidence of upper respiratory illness in a study of 29 male cyclists. Crooks et al.[69,70] observed similar trends. Lindbaek et al.[40] performed a randomized placebo-controlled study comparing the effects of bovine colostrum and placebo on illness duration in patients with nonstreptococcal sore throat, but results were presented for a single cohort and few details of the trial were provided.

Patel and Rana[39] conducted an open-label, noncomparative study of 3 g of daily bovine colostrum supplementation in 551 children after recurrent episodes of URTI or diarrhea during the previous 6 months. Colostrum was supplied as a powder (Pedimune; Merck Ltd, Mumbai, India). The number of URTI episodes was reduced by 73.0%, 83.3%, and 91.2% at 4, 8, and 12 weeks, respectively, compared with the number of episodes in the first 6 months prior to enrollment. The number of diarrhea episodes and the frequency of hospitalization for URTI or diarrhea were also significantly reduced.[39] Other authors, however, have pointed out the numerous limitations and poor methodological quality of this study.[95] First, it used an open, uncontrolled design that relied only on self-reported symptoms. Second, the authors appear to have compared the rates of URTI and diarrhea at 4, 8, and 12 weeks with baseline values collected over 6 months without converting them to monthly rates, which unsurprisingly yielded results indicating significantly fewer episodes. Thus, the results of this study require cautious interpretation.

Patiroglu and Kondolot[41] investigated the administration of an oral lozenge (Igazym; ASSOS Ltd, Vejle, Denmark) containing 14 mg of colostrum and 2.2 mg of lysozyme or a placebo lozenge 3 times per day for 1 week in 31 children aged 5–16 years with known IgA deficiency and clinical signs of URTI. The presence of viral infection was determined clinically, and etiologies were not confirmed by laboratory investigation. No difference in serially tested salivary IgA levels was observed between groups, but 1 week of colostrum supplementation reduced infection severity scores compared with placebo. Similarly, 43.8% of patients in the colostrum group and 13.3% in the placebo group reported cessation of symptoms, but this difference was not significant.[41] Finally, McClead et al.[37] observed no difference in stool frequency in adult males infected with *Vibrio cholerae* who received defatted, casein-precipitated bovine colostrum, hyperimmune bovine colostrum, or water, while Huppertz et al.[42] demonstrated a significant reduction in stool frequency in an RT of 30 children with diarrhea caused by *E. coli* expressing Shiga toxin (Stx) 1, Stx2, both Stx1 and Stx2, intimin, or enterohemorrhagic *E. coli* (EHEC) hemolysin. The colostrum preparation used, Lactobin,[88] was compared with placebo. The composition of the placebo was not specified in the paper.

These data suggest that bovine colostrum has a prophylactic effect against URTI, which may correspond to the findings of increased salivary IgA levels in athletes receiving colostrum supplementation. These data, however, are primarily self-reported and were obtained by pooling study results that were not individually significant. The studies are heterogeneous with regard to population, colostrum dosage and formulation, methodological quality, and results. Thus, this effect of bovine colostrum must be confirmed in further well-designed, prospective, placebo-controlled studies.

Two studies investigating the effect of bovine colostrum on the immune response to immunization in healthy subjects were identified.[44,45] He et al.[44] conducted a randomized study in 18 healthy subjects receiving 100 mL of sterile filtered bovine colostrum (Bioenervi) per day for 7 days or water colored with riboflavin food color. On days 1, 3, and 5, the volunteers received oral vaccines against *Salmonella typhi* Ty21a. No significant difference in IgA, IgG, IgM, Fcγ, or complement receptor expression on neutrophils and monocytes was observed between groups. The authors noted a trend toward a greater increase in specific IgA among subjects receiving bovine colostrum.

In a double-blind, placebo-controlled RT,[45] 138 healthy volunteers receiving 1.2 g of bovine colostrum, a mixture of micronutrients, bovine colostrum plus micronutrients, or placebo were given tetanus toxoid and typhoid vaccines after 6 weeks of supplementation. Supplementation with bovine colostrum had no effect on the immune parameters assessed. The bovine colostrum concentrate (Proventra; GalaGen Inc., Minnetonka, MN, USA) was a spray-dried, sterile filtered powder from the whey fraction of nonspecific bovine colostrum, and the placebo was an isocaloric powdered drink based on skim milk powder, sugar, and maltodextrin. In another randomized study,[43] supplementation with 480 mg of colostrum 2 times per day significantly reduced secretory IgA levels in 20 healthy volunteers. These contradictory results may be attributable to the use of test subjects with good health and nutritional status and without exercise-induced immune perturbation. In a recent single-dose crossover RT, Jensen et al.[46] tested the effect of a low-molecular-weight immunoglobulin-depleted fraction of bovine colostrum or a rice flour placebo in 12 healthy subjects, finding increased phagocytic activity of monocytes and polymorphonuclear cells, an increased white blood cell count, and a transient decrease in the circulation of natural killer cells, while Appukutty et al.[72] found modulated in vitro interferon-γ activity after 6 weeks of colostrum supplementation in adolescent athletes. These results suggest that bovine colostrum may, after contact with the gut mucosa, trigger immunological events that are followed by systemic effects.

Short bowel syndrome

SBS is characterized by malabsorption and consequent malnutrition in patients devoid of parts of the small intestine as the result of massive surgical resection or congenital defects. Intestinal adaptation after small bowel resection is believed to be pivotal in the ability of patients to sufficiently absorb fluid, electrolytes, and nutrients and may be influenced by several factors, including peptide growth factors, growth hormones, and luminal nutrients.[96] The high amounts of intestinotrophic factors in colostrum have generated research interest in the hope that colostrum supplementation might improve intestinal adaptation and absorption in patients with SBS.

In an animal study of 4-week-old piglets that underwent small bowel resection, colostrum feeding increased villus height and crypt depth.[97] In similar studies using a preclinical piglet model of SBS, investigators found that colostrum supplementation increased circulating levels of glucagon-like peptide 2, IGF-1, and IGF binding protein 2 and resulted in weight gain and muscle hypertrophy, leading them to suggest the possibility of enhanced postoperative intestinal adaptation in colostrum-fed pigs.[98,99] Nevertheless, while some studies have suggested that colostrum improves intestinal adaptation after small bowel resection, others have not been able to confirm this finding.[100]

Two studies, one in adults[34] and one in children,[35] examining the possible beneficial effect of bovine colostrum in SBS were identified. In both studies, the investigators used whole colostrum sterilized by electron beam irradiation. The placebo was prepared as a nutrient-matched mix of semi-skimmed milk, cream, and whey protein powder. Lund et al.[34] investigated the effects of 250 mL of colostrum and control supplementation twice per day on intestinal function and adaptation in adult patients with SBS using a randomized, double-blind, crossover design. The treatments were separated by a 4-week washout period. Complete datasets were obtained from 8 of 12 patients, and colostrum was not superior to the control supplement.[34] In another placebo-controlled crossover RT in 9 clinically stable children with SBS,[35] 20% of the daily enteral fluid intake was replaced with bovine colostrum and a milk-mix control diet, separated by a 4-week washout period. Colostrum did not improve energy or wet-weight absorption in metabolic balance studies, growth evaluated by knemometry (a noninvasive technique of lower leg length measurement used for the study of short-term growth), or levels of IGF-1 or IGF binding protein 3. After colostrum supplementation, all subjects reported firmer feces and less frequent daily defecation. However, the mean weight of feces did not differ between the two diets.[35]

Although few human studies have examined the effects of colostrum on SBS, and the results are thus inconclusive, no evidence of a marked effect on intestinal function has been documented in this patient group. Evidence from animal studies showing the beneficial properties of colostrum in SBS is based on studies in newly operated animals, suggesting that intestinal adaptation leading to functional and structural changes is more plausible.[98] The capacity of bovine colostrum to facilitate such changes in the human intestine has yet to be determined.

The absence of a beneficial effect in clinically stable patients with SBS is in line with the notion that bovine colostrum supplementation may be most beneficial during inflammation and/or mucosal damage[17] and corresponds to the findings of earlier studies demonstrating that bovine colostrum does not affect intestinal nutrient absorption in healthy adults.[60]

Disorders of growth and metabolism

In a recent study conducted in mice with streptozotocin-induced diabetes, an IGF-rich bovine colostrum fraction significantly reduced blood glucose and improved organ weights, suggesting that this fraction may be valuable in the treatment of patients with diabetes.[101] This review identified one study examining metabolic control in patients with diabetes.[36] Sixteen patients with type 2 diabetes ingested 5 g of pasteurized, powdered bovine colostrum (Immuno-Dynamics, Inc., Fennimore, WI, USA) twice daily for 4 weeks and were followed longitudinally; the same patients served as pre- and postinterventional controls. The authors found a continuous decrease in postprandial blood glucose levels throughout the study period. Total cholesterol, triglyceride, and ketone body levels also decreased significantly. Although these findings suggest that bovine colostrum has a positive effect on metabolic control in type 2 diabetes, the mechanisms and actual benefit remain unestablished.

The possible anabolic effect and the potential ability of colostrum to improve nutrient absorption have led to speculation about the usefulness of colostrum supplementation in managing failure to thrive. In a single-blind clinical RT in 120 children diagnosed with nonorganic failure to thrive, subjects received 40 mg/kg/day bovine colostrum for 3 months or standard care. Colostrum was supplied as capsules containing pasteurized lyophilized bovine colostrum. Supplementation significantly improved the Gomez, but not the Waterlow, index of growth insufficiency.[47] The study is inconclusive with regard to the possible role of bovine colostrum supplementation in nonorganic failure to thrive because the results are contradictory and the study has obvious weaknesses, such as the single-blind design and the lack of a placebo group.

Juvenile idiopathic arthritis

One randomized, placebo-controlled study evaluating the effect of sterile, filtered, freeze-dried bovine colostrum versus a human *Lactobacillus* strain GG or hyperimmune bovine colostrum on juvenile chronic arthritis showed no clinical effect or paraclinical outcomes relevant for disease control. It did show increased urease activity in colostrum-treated patients,[49] but the implication of this finding is not clear.

Irritable bowel and chronic pain syndromes

One RT evaluating the effect of bovine colostrum (Immuno-Dynamics) on irritable bowel syndrome was identified. The study was placebo controlled, but the nature of the placebo was not stated. The study included 110 adult patients and showed no significant effect of colostrum supplementation at the end of the study period.[48]

One case series evaluated the effect of bovine colostrum (Lactobin[88]) on chronic pain syndrome.[50] The authors suggested that colostrum induced apoptosis regulation in monocytes in these patients, but this conclusion relied on in vitro evidence from four patients and should be interpreted cautiously.

Dosage and formulation of supplementation

The optimal dosage and duration of bovine colostrum supplementation have not been established. Most studies have been conducted in healthy adults using doses that range from 14 mg 3 times per day to 60 g daily. Few studies have directly compared different dosage regimens.[54,64] Furthermore, standardization of bioactivity, which is influenced by breed, herd, milking times, and formulation, is complicated and has not been attempted consistently.[12,13] Thus, simple expressions of dosage in weight units are not sufficiently informative with regard to the bioactivity of the constituents of colostrum.

Several commercial colostrum products are available,[5] a number of which were used in the studies reviewed here, including Lactobin (Biotest Pharma), a spray-dried immunoglobulin-enriched powder[88]; Intact (Numico Research Pty Ltd), a low-heat, low-fat, low-lactose concentrated bovine colostrum powder; Pedimune colostrum powder (Merck); ColoPlus (ColoPlus AB), a porridge containing 32% bovine colostrum; Dynamic colostrum (Hi-Col), a freeze-dried colostrum powder; a powdered whole colostrum (Symbiotics); Bioenervi (Viable Products), a sterile, filtered, colostrum-based product; a pasteurized, powdered bovine colostrum (Immuno-Dynamics); IgG Plus (Smart-Naco, Kuala Lumpur, Malaysia); and Igazym (ASSOS Ltd), a lozenge containing bovine colostrum and lysozyme.

Some studies used a complete colostrum product, whereas others used fractions or concentrated formulations, with concentrations consisting primarily of protein and IgG. Most authors have reported the protein and/or IgG content of formulations, rendering this the only comparable operational parameter among studies. However,

different dairy processes, such as heat treatment, ultrafiltration, freeze-drying, and the removal of lipid, casein, lactose, and salts, affect the bioactive components of bovine colostrum. An overview of the effect of different processing steps can be found in the work of Elfstrand et al.[13] The use of concentrated formulations may preclude the inclusion of other possibly bioactive and immunologically active substances. Thus, formulation and sterilization methods should be considered and reported.

Bioactive compounds of interest may vary with the focus of research. Although the effect of bovine colostrum may depend on the concentration of a specific constituent for a particular condition, possible benefits may also rely on the combined effects of various factors. Thus, the effective dose may depend on the condition or outcome as well as the subjects or population studied. Table 2 compares the colostrum dosage and the protein and IgG contents in studies included in this review. It may serve as a guide for determining such contents and dosage in future studies.

Furthermore, when reading or planning studies that evaluate the effects of bovine colostrum, considerations about the optimal choice of control supplement may be important. In the majority of the studies included in this review, the investigators used either whey protein powder or a mix of milk powder and protein powder. It seems important that, with regard to macronutrient composition, control supplements either be similar or isocaloric and matched.

Safety and adverse effects

There were no reports of serious side effects or toxicities in the 51 studies, which included a total of 2,326 participants. Reported side effects were mild and included complaints of an unpleasant taste, nausea, flatulence, diarrhea, skin rash, and unspecified abdominal discomfort.[28,29,34,39,66,69] Nine studies specifically reported an absence of side effects.[26,30,33,41,42,47,55,74] In general, bovine colostrum is considered safe and well tolerated.[21,102]

FUTURE PERSPECTIVES

Many questions about the effects and mechanisms of action of bovine colostrum remain unanswered. Currently available data suggest that most benefits of bovine colostrum derive from its immune-modulating capabilities, which are utilized in the maintenance or improvement of host defenses under different detrimental conditions or immune system exposures, or its ability to aid in the maintenance of GI mucosal integrity by suppressing gut inflammation and promoting mucosal tissue repair.[26,28–31,33,38,41] Among the numerous future applications of bovine colostrum, some have been highlighted as warranting additional attention.[11]

Necrotizing enterocolitis (NEC) is a common and devastating disease in the preterm neonate that compromises GI integrity and function. Nutrition is considered important in the prevention and management of NEC.[103] In the present review, no eligible study examining the use of bovine colostrum in patients with NEC or neonatal septicemia was identified. However, such treatment may become an area of interest,[11] as animal studies using bovine colostrum and human trials using bovine lactoferrin have been conducted.[1,5,75,76,104–106] Most convincingly, the beneficial effects of bovine colostrum have been demonstrated repeatedly in a well-established piglet model of preterm infants. Colostrum was superior to infant formula as the initial diet because it improved both gut maturation and resistance against bacterial infection and NEC.[1,104,106,107] Thus, bovine colostrum or derivatives thereof should be considered when developing novel therapeutic strategies for the prevention of NEC and sepsis in preterm infants. When planning studies using bovine colostrum in infants, there may be concern that exposure to cow milk protein before the age of 6 months increases the risk of cow milk allergy, particularly in predisposed infants. All protocols should ask for parental heredity, as the majority of the allergic babies have one or two parents who have atopic disease, and infants positive for this variable should not be given the product.[108] The use of colostrum at this age should preferably be restricted to infants with specific symptoms or circumstances, such as prematurity.

Furthermore, when considering nutritional interventions in full-term and premature infants, the aspect of growth is important because the optimal feeding strategy may influence not only growth but also neurocognitive outcomes.[109] Colostrum contains a mixture of proteins, such as immunoglobulin, and a range of growth factors. This mixture does not necessarily promote rapid growth, but its potential to accelerate growth needs further study.

Bovine colostrum has been proposed to play a role in the treatment or prevention of chemotherapy-induced mucositis, and evidence suggests possible beneficial effects on the oral mucosa.[11] Intestinotrophic factors in bovine colostrum may promote epithelial integrity and tissue repair, and antimicrobial proteins and peptides may have direct antimicrobial and endotoxin-neutralizing capabilities and reduce gut inflammation and microbial translocation. Administration of cheese whey extract to methotrexate-treated rats improved intestinal morphology and function in the treated animals. Similar results were seen in colostrum-fed, busulfan-treated, and cyclophosphamide-treated piglets.[110,111] A study designed to investigate the effect of bovine colostrum on GI

Table 2 **Overview of colostrum dosage and corresponding protein and IgG content in studies of enterally ingested bovine colostrum.**

Reference	Ratio of protein/IgG	Dosage	Protein content	IgG content	Effect (Y/N)
NSAID- and surgery-induced gut damage					
Playford et al. (2001)[26]	4.3 g/L/–	375 mL	1.6 g	–	Y
Playford et al. (2001)[26]	4.3 g/L/–	375 mL	1.6 g	–	N
Bolke et al. (2002)[32]	80/65[a]	42 g	33.6 g	27.3 g	N
Bolke et al. (2002)[33]	80/65[a]	56 g	44.8 g	36.4 g	Y
HIV-associated diarrhea and immunosuppression					
Saxon and Weinstein (1987)[27]	–/–	1–5 L	–	–	N
Rump et al. (1992)[28]	–/60	10 g	–	6 g	Y
Plettenberg et al. (1993)[29]	–/45	10 g	–	4.5 g	Y
Flóren et al. (2006)[30]	23[b]/7.4	32 g	23 g	7.4 g	Y
Kaducu et al. (2011)[31]	23[b]/7.4	32 g	23 g	7.4 g	Y
Sports nutrition and exercise					
Antonio et al. (2001)[51]	79/–	20 g	15.8 g	–	Y
Coombes et al. (2002)[54]	75/15[c]	20 g or 60 g	15/45 g	3/9 g	Y
Buckley et al. (2002)[56]	75/15[c]	60 g	45 g	9 g	Y
Hofman et al. (2002)[74]	75/15[c]	60 g	45 g	9 g	Y
Brinkworth et al. (2002)[59]	75/15[c]	60 g	45 g	9 g	Y
Kuipers et al. (2002)[73]	75/15[c]	60 g	45 g	9 g	N
Fry et al. (2003)[62]	75/15[c]	60 g	45 g	9 g	N
Buckley et al. (2003)[57]	75/15[c]	60 g	45 g	9 g	Y
Brinkworth & Buckley (2003)[60]	75/15[c]	60 g	45 g	9 g	N
Brinkworth & Buckley (2004)[61]	75/15[c]	60 g	45 g	9 g	N
Brinkworth et al. (2004)[58]	75/15[c]	60 g	45 g	9 g	Y
Mero et al. (2005)[63]	30/22.5	20 g	6 g	4.5 g	Y
Shing et al. (2006)[53]	75/15[c]	10 g	7.5 g	1.5 g	Y
Kerksick et al. (2007)[66]	–/–	60 g	–	–	Y
Immune functions in sport and exercise					
Mero et al. (1997)[64]	–/0.39 g/L	125/25 mL	–	0.05 g/0.01 g	Y
Mero et al. (2002)[65]	30/22.5	20 g	6 g	4.5 g	Y
Crooks et al. (2006)[69]	33/–[d]	10 g	8.6 g	–	Y
Shing et al. (2007)[52]	–/20	10 g	–	2 g	Y
Buckley et al. (2009)[55]	75/15[c]	60 g	45 g	9 g	Y
Davison & Diment (2010)[68]	52/–	20 g	10.4 g	–	Y
Crooks et al. (2010)[70]	31.6/2.9[d]	20 g	6.32 g	0.58 g	N
Marchbank et al. (2011)[67]	80/15–20	20 g	16 g	3–4 g	Y
Carol et al. (2011)[71]	–/–	25 g	–	–	N
Appukutty et al. (2011)[72]	–/–	20 g	–	–	Y
Infection and immune responses					
McClead et al. (1988)[37]	–/–	4 g	–	–	N
McClead et al. (1988)[37]	–/–	16 g	–	–	N
Huppertz et al. (1999)[42]	80/65[a]	21 g	16.8 g	13.7 g	Y
He et al. (2001)[44]	–/–	–	–	–	N
Brinkworth & Buckley (2003)[38]	75/15[c]	60 g	45 g	9 g	Y
Patel & Rana (2006)[39]	–/–	3 g	–	–	Y
Lindbaek et al. (2006)[40]	–/–	–	–	–	N
Wolvers et al. (2006)[45]	–/–	1.2 g	–	≈0.5 g	N
Patiroglu & Kondolot (2013)[41]	–/–[e]	0.042 g	–	–	Y
Mikic et al. (2012)[43]	–/–	0.96 g	–	–	Y
Jensen et al. (2012)[46]	–/–	–	–	–	Y
Short bowel syndrome					
Lund et al. (2012)[34]	106/50 g/L[f]	500 mL	53 g	25 g	N
Aunsholt et al. (2012)[35]	110/35 g/L[g]	20% of intake	–	–	N
Growth and metabolic disorders					
Kim et al. (2009)[36]	56.6/26	10 g	5.66 g	2.6 g	Y
Panahi et al. (2010)[47]	–/–	40 mg/kg	–	–	Y
Juvenile idiopathic arthritis					
Malin et al. (1997)[49]	–/39	10 g		3.9 g	Y
Chronic pain syndrome and irritable bowel syndrome					
Ragab et al. (2007)[48]	–/–	–	–	–	N
Waaga-Gasser et al. (2009)[50]	–/–	1–20 g	–	–	Y

Abbreviations and symbols: –, Not stated; N, no; NSAID, nonsteroidal anti-inflammatory drug; Y, yes.
[a] Total immunoglobulin content, not only IgG.
[b] Protein content of full product containing 32% bovine colostrum.
[c] Not stated in all manuscripts, but referenced here.[18]
[d] Also contains protein from other sources.
[e] Also contains lysozyme.
[f] IgG content stated to >50 mg/mL.
[g] IgG content stated to >3.5%. In some manuscripts, it may not be clear whether the IgG content is expressed as an absolute value or as a percentage of the total protein content.

toxicity in children receiving chemotherapy is currently under way (www.clinicaltrials.gov, identification number: NCT01766804).

Studies of primary Sjögren's syndrome and oral lichen planus have provided support for the role of topically applied bovine colostrum in oral mucosa maintenance.[77] Such topical application, although not considered in this review, may be a novel approach to alleviate oral manifestations of these diseases. The use of bovine colostrum in the treatment of inflammatory bowel disease has received little attention, and this review identified no such eligible trial, but colostrum enemas ameliorated symptoms of distal colitis in one trial.[80] These data support the role of topical bovine colostrum application in inflammatory bowel disease and point to the need for further randomized controlled studies of sufficient power.

CONCLUSION

In the present review, 49 publications reporting on 51 clinical studies in which bovine colostrum was used as a dietary supplement were identified. The studies are heterogeneous with regard to methodological quality, colostrum dosage and preparation, populations, and outcomes studied, and most studies focused on improving performance or immunological status in healthy populations. Most studies used surrogate markers to study the effects of bovine colostrum, and little evidence supports an actual clinical benefit of colostrum supplementation. Studies suggesting clinical benefits were generally of poor methodological quality, and most findings remain unconfirmed.

Evidence suggests that bovine colostrum has immune-modulating capabilities that may be utilized in maintaining or improving host defenses under different detrimental conditions or immune system exposures. Bovine colostrum also appears to play a role in the maintenance of GI mucosal integrity via antimicrobial and endotoxin-neutralizing effects, the suppression of gut inflammation, and the promotion of mucosal tissue repair. Furthermore, after contact with the gut mucosa, bovine colostrum may trigger immunological events that lead to systemic effects. Thus, even though no conclusion regarding clinical benefit can be drawn, there is a need to conduct more studies with colostrum, which appears to provide benefit in some conditions. Further preclinical and translational research utilizing animal models may expand current knowledge regarding the importance of measurable immunological and GI outcomes and aid the selection of relevant populations and interventions for clinical studies. Well-controlled, sufficiently powered clinical studies aimed at establishing a clinical benefit of bovine colostrum supplementation are warranted.

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Declaration of interest. The authors have no relevant interests to declare.

Authors' contributions. MR and SH conceived the idea and designed the study. MR performed the literature search, carried out quality assessment, and drafted and finalized the manuscript. SH, PTS, and KM critically reviewed the manuscript. All authors approved the final version submitted for publication.

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