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Bovine Colostrum for Veterinary and Human Health Applications: A Critical Review

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Abstract

Bovine colostrum harbors a diverse array of bioactive components suitable for the development of functional foods, nutraceuticals, and pharmaceuticals with veterinary and human health applications. Bovine colostrum has a strong safety profile with applications across all age groups for health promotion and the amelioration of a variety of disease states. Increased worldwide milk production and novel processing technologies have resulted in substantial growth of the market for colostrum-based products. This review provides a synopsis of the bioactive components in bovine colostrum, the processing techniques used to produce high-value colostrum-based products, and recent studies utilizing bovine colostrum for veterinary and human health.

1. INTRODUCTION

Colostrum is the initial mammary secretion post-parturition, bestowing a complete nutritional profile and bioactive compounds vital for optimum nutrition and promoting the growth, development, and immunological defense of newborns. The composition, structure, and physicochemical properties of colostrum fluctuate significantly across different species (Roy et al. 2020). For this review, colostrum, unless otherwise defined, will refer to milk from dairy cows up to 3 days postpartum (McGrath et al. 2016). Calves are agammaglobulinemic at birth, as the syndesmochorial placenta of cows prevents passive immunity transfer from the mother to the neonate during gestation. As a result, bovine colostrum contains high concentrations of bioactive compounds, particularly immunoglobulin G (IgG), to provide passive immunity. In addition, colostrum is rich in growth factors, lactoperoxidase, lysozyme, lactoferrin, cytokines, vitamins, peptides, leukocytes, hormones, minerals, and oligosaccharides. These components engage in a plethora of biological responses, including maturation of the gastrointestinal (GI) tract, immune functioning, energy homeostasis, and protection against pathogens (Lopez & Heinrichs 2022). To acquire passive immunity, newborn calves require at least 4 L of first-milking colostrum within 1–2 hours of birth, with an IgG concentration of more than 50 g/L (Godden et al. 2019). The enterocytes of the calf small intestine freely absorb IgG and other large molecules by pinocytosis for the first 6–12 hours postpartum, before intestinal permeability ceases at 24 hours (Lopez & Heinrichs 2022). Colostrum accounts for ∼1% of a healthy cow's annual milk production, far in excess of the calves' needs (Scammell & Billakanti 2022). Colostrum's bioactive components possess cross-species bioactivity, making it an attractive choice in the research and development of functional foods and pharmaceuticals with veterinary and human applications (Playford & Weiser 2021). The market for colostrum products is developing rapidly and is projected to increase from $2.6 billion in 2019 to $4.3 billion in 2027, largely due to improved processing techniques and novel methods for the isolation and identification of previously concealed colostrum constituents (Sydney et al. 2022). A plethora of preclinical and clinical studies in humans have demonstrated the therapeutic benefits of colostrum supplementation for health promotion and the treatment of numerous diseases (Kaplan et al. 2021). Colostrum products have also been explored for use in animal husbandry and for the health and well-being of large animals and domestic pets (Pagnoncelli et al. 2022). This review describes the bioactive composition of colostrum, current methods used to produce colostrum-based products, and, finally, recent studies of colostrum supplementation for veterinary and human health applications. An overview of the applications of bovine colostrum in veterinary and human health is presented in **Figure 1**.

2. THE BIOACTIVE COMPOSITION OF BOVINE COLOSTRUM

The composition and physical properties of colostrum are highly variable due to factors such as individuality, age, breed, nutrition, antibiotics, and disease exposure (Scammell & Billakanti 2022). Generally, colostrum contains more fat, protein, vitamins, minerals, hormones, growth factors, cytokines, and nucleotides and less lactose than mature milk (McGrath et al. 2016). With the exception of lactose, all these compounds decrease rapidly during the first 3 days of lactation before transitioning to mature milk (Playford & Weiser 2021). The gross chemical and physical composition of colostrum is shown in **Table 1**.

2.1. Protein

The protein concentration of colostrum is 15% (weight/weight), falling to 3% in mature milk (Sats et al. 2020). Immunoglobulins (IgG, IgA, IgE, IgD, and IgM) constitute 70–80% of the protein in colostrum, with IgG accounting for 80–85% of the total immunoglobulin content (Playford

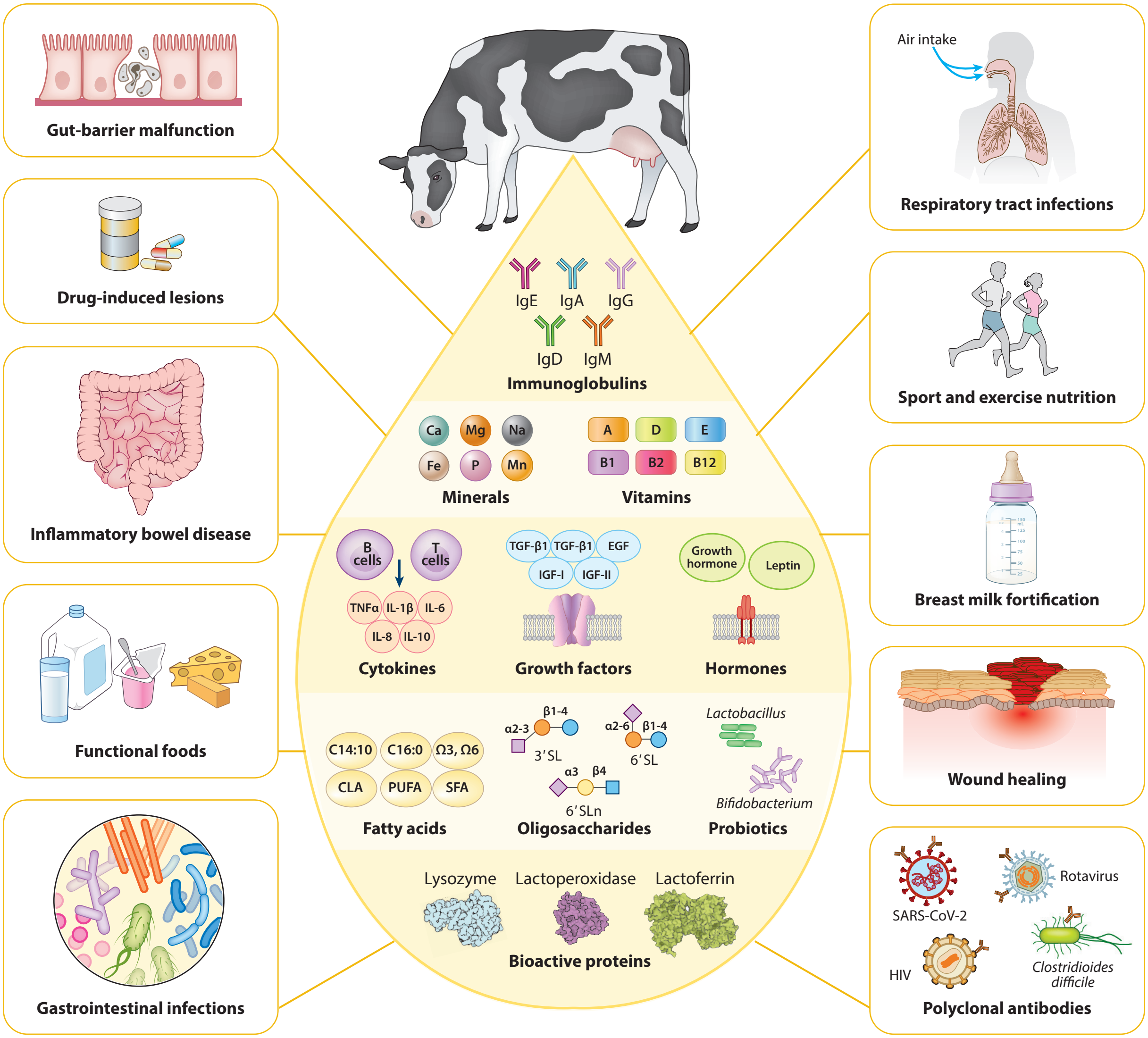

Figure 1

An overview of the bioactive composition and applications of bovine colostrum in veterinary and human health. Figure adapted from images created with BioRender.com. Abbreviations: CLA, conjugated linoleic acid; EGF, epidermal growth factor; IgA, immunoglobulin A; IgD, immunoglobulin D; IgE, immunoglobulin E; IGF, insulin-like growth factor; IgG, immunoglobulin G; IgM, immunoglobulin M; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; SL, sialyllactose; SLn, siayllactosamine; TGF, transforming growth factor.

& Weiser 2021). The total immunoglobulin content of colostrum ranges from 42 to 90 g/L and falls to 0.4–0.9 g/L in mature milk. Immunoglobulins (antibodies) are glycoproteins produced by B cells of the immune system that specifically recognize and bind antigens present on bacteria and viruses (Ulfman et al. 2018). These Y-shaped molecules consist of four polypeptide chains, with two identical heavy chains and two identical light chains connected via disulfide bonds. Antigen binding to the two antigen binding fragments (Fab) of the N-terminal region causes immune complex formation and activation (Ghosh & Iacucci 2021). The C-terminal region consists of

Table 1 Concentrations of select macronutrients, micronutrients, immunoglobulins, and general antimicrobial peptides present in bovine colostrum and mature milk

Component	Colostrum	Milk
Total solids (%)	24–28	12.9
Fat (%)	6–7	3.6–4.0
Protein (%)	14–16	3.1–3.2
Casein (%)	4.8	2.5–2.6
Lactose (%)	2–3	4.7–5.0
Immunoglobulins	**Colostrum**	**Milk**
IgG1 (g/L)	34.0–87.0	0.31–0.40
IgG2 (g/L)	1.6–6.0	0.03–0.08
IgA (g/L)	3.2–6.2	3.2–6.2
IgM (g/L)	3.7–6.1	0.03–0.06
Proteins	**Colostrum**	**Milk**
Lactoferrin (g/L)	1.5–5	0.02–0.75
Lactoperoxidase (mg/L)	11–45	13–30
Lysozyme (mg/L)	0.14–0.7	0.07–0.6
Growth factors	**Colostrum**	**Milk**
Epidermal growth factor (ng/mL)	4–325	1–150
Insulin-like growth factor-I (ng/mL)	100–2,000	5–100
Insulin-like growth factor-II (ng/mL)	150–600	5–100
Transforming growth factor-β1 (ng/mL)	1–50	<5
Transforming growth factor-β2 (ng/mL)	150–1,150	10–70
Minerals	**Colostrum**	**Milk**
Calcium (g/kg)	2.6–4.7	1.2–1.3
Phosphorus (g/kg)	4.5	0.9–1.2
Potassium (g/kg)	1.4–2.8	1.5–1.7
Sodium (g/kg)	0.7–1.1	0.4
Magnesium (g/kg)	0.4–0.7	0.1
Zinc (mg/kg)	11.6–38.1	3.0–6.0
Fat	**Colostrum**	**Milk**
SFAs (g/100 g)	66.12–74.05	64.88–64.47
MUFAs (g/100 g)	24.54–30.09	31.51–31.79
PUFAs (g/100 g)	3.79–3.88	3.61–3.74
Vitamins	**Colostrum**	**Milk**
Thiamin (B1) (μg/mL)	0.58–0.90	0.4–0.5
Riboflavin (B2) (μg/mL)	4.55–4.83	1.5–1.7
Niacin (B3) (μg/mL)	0.34–0.96	0.8–0.9
Cobalamin (B12) (μg/mL)	0.05–0.60	0.004–0.006
Vitamin A (μg/100 mL)	25	34
Vitamin D (IU/g fat)	0.89–1.81	0.41
Tocopherol (E) (μg/g)	2.92–5.63	0.06
Carbohydrates	**Colostrum**	**Milk**
3′-sialyllactose (g/L)	0.42–1.24	0.13
6′-sialyllactose (g/L)	0.05–0.13	0.04
6′-sialyl-N-acetyllactosamine (g/L)	0.07–0.42	0.01

Ranges are shown where available. Values obtained from Arslan et al. (2021), Bunyatratchata et al. (2021), and Playford & Weiser (2021).

Abbreviations: MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids.

two nonantigen binding fragments, termed the fragment crystallizable (Fc) region. The Fc region interacts with Fc receptors present on immune effector cells such as phagocytes, natural killer cells, dendritic cells, and $CD4^+$ T lymphocytes (Ghosh & Iacucci 2021). This process presents pathogens to macrophages for destruction, activates T cells and B cells, modifies the intestinal microbiota, and induces local IgA production (Ulfman et al. 2018). Specific vaccination of cows against human or bovine pathogens (hyperimmunization) results in the production of polyclonal, pathogen-specific antibodies in colostrum secretions, commonly referred to as hyperimmune bovine colostrum (HBC) (Ulfman et al. 2018). HBC products have been shown to effectively neutralize a range of pathogens, including rotavirus, *Escherichia coli*, *Cryptosporidium*, *Shigella*, *Vibrio cholerae*, *Clostridioides difficile*, *Helicobacter pylori*, human immunodeficiency virus (HIV), *Candida albicans*, and *Streptococcus mutans* (Borad & Singh 2022). Lactoperoxidase is an antimicrobial glycoprotein and a member of the heme peroxidase family of enzymes, which are known to inhibit bacterial metabolism. Lactoperoxidase catalyzes the oxidation of thiocyanate ions, at the expense of hydrogen peroxide, to generate reactive products that are toxic to numerous gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Listeria monocytogenes*, and *Staphylococcus aureus* (Wolfson & Sumner 1993). Concentrations of lactoperoxidase in colostrum (11–45 mg/L) are comparable to milk (13–30 mg/L), but the activity of lactoperoxidase is substantially higher in colostrum (McGrath et al. 2016). Lysozyme is an antimicrobial enzyme that lyses the peptidoglycan layer of gram-positive and gram-negative bacterial cells by hydrolysis to cause cell lysis. Lysozyme concentrations in colostrum (0.14–0.7 mg/L) are higher than in mature milk (0.07–0.6 mg/L) (McGrath et al. 2016). Lactoferrin is also found in colostrum and is an iron-binding glycoprotein and member of the transferrin family. Lactoferrin induces multiple valuable biological effects, including iron absorption, immune modulation, enhancement of the antimicrobial activity of lysozyme, and increase in the growth of epithelial cells and fibroblasts (Zhao et al. 2019). Colostrum is routinely used for the isolation of lactoferrin to add to infant formula, cosmetics, and nutritional supplements (Sydney et al. 2022).

2.2. Carbohydrates

Lactose is the predominant carbohydrate in colostrum (2.5%) and is present at lower concentrations than in mature milk (5%) (McGrath et al. 2016). Oligosaccharides are the third most abundant solid component found in milk after lactose and lipids (Fong et al. 2011). These structurally and biologically diverse molecules, although resistant to digestion, are associated with various beneficial functions (Fong et al. 2011). Oligosaccharide concentrations are significantly higher in colostrum (0.7–1.2 g/L) than in mature milk (0.1 g/L) (ten Bruggencate et al. 2014). 3′ Sialyllactose (3′SL), 6′ sialyllactose (6′SL), 6′ siayllactosamine (6′SLN), and disialyllactose (DSL) are the major bovine colostrum oligosaccharides (BCOs), with 3′SL accounting for 70% of the oligosaccharide content in colostrum (Bunyatratchata et al. 2021). BCOs exert prebiotic effects by acting as metabolic substrates for beneficial bacteria such as bifidobacteria, which are important early colonizers of the calf gut (Bondue et al. 2016). Furthermore, BCOs act as competitive inhibitors to pathogenic bacteria (e.g., *E. coli*, *Cronobacter sakazakii*, and *H. pylori*) for binding sites on gut epithelial cells by mimicking epithelial cell surface carbohydrates (Morrin et al. 2019, 2020). Advancements in enzymatic glycosylation have provided opportunities to alter the structure of bovine milk oligosaccharides to better resemble human milk oligosaccharides (Weinborn et al. 2020). Colostrum is also rich in glycosylated proteins, especially bovine glycomacropeptide, which has different glycosylated forms and is created via κ-casein proteolysis during digestion (McGrath et al. 2016). Bovine glycomacropeptide has bifidogenic activity, as shown by its concentration-dependent growth promotion of *Bifidobacterium longum* subspecies *infantis* (O'Riordan et al. 2018).

Colostrum also contains β-lactoglobulin, a whey protein with numerous human health benefits that is absent in human colostrum (Le Maux et al. 2014).

2.3. Fats

The fat component of colostrum is usually removed to facilitate commercial processing; however, it is not biologically inert and contains multiple beneficial components. Colostrum contains ~7% fat, predominantly comprising milk-fat globules (Sats et al. 2022). There are lower concentrations of *trans*-fatty acids and short-chain fatty acids (C4–C10) in colostrum than in mature milk (Contarini et al. 2014). Colostrum contains approximately 65–75% saturated fatty acids (SFAs), 24–28% monounsaturated fatty acids (MUFAs), and 4–5% polyunsaturated fatty acids (PUFAs) (O'Callaghan et al. 2020, Wilms et al. 2022). Ω3 and Ω6 PUFAs are up to 25% higher in colostrum than mature milk (Wilms et al. 2022). Oleic acid (C18:1n-9), myristic acid (C14:0), and palmitic acid (C16:0) are the predominant fatty acids in colostrum (O'Callaghan et al. 2020, Wilms et al. 2022). Palmitate is important in early life nutrition (Miles & Calder 2017), and oleic acid has been shown to exert beneficial effects in immunomodulation and cardiovascular health (Sales-Campos et al. 2013). Colostrum from primiparous cows has a significantly higher level of conjugated linoleic acid (CLA; *cis*-9, *trans*-11) than that from multiparous cows; however, there are no overall differences between colostrum and mature milk (O'Callaghan et al. 2020, Wilms et al. 2022). CLA has attracted attention for its apparent benefits, including reduction of carcinogenesis, atherosclerosis, inflammation, obesity, and diabetes demonstrated in human and animal models (Yang et al. 2015). Further studies on the fat composition of colostrum are needed to allow the segregation of colostrum from mature milk. This information would minimize the undesirable mixing of raw milk with colostrum before processing, enable more efficient and targeted production of colostrum-based foods and food supplements, and avoid processing-related issues that have previously been reported with colostrum (Tsioulpas et al. 2007).

2.4. Vitamins, Minerals, and Hormones

The concentrations of fat-soluble vitamins (A, D, E) and carotenoids, as well as those of the water-soluble vitamins thiamine, riboflavin, vitamins B_1, B_2, B_6, and B_{12}, folate, and vitamin C, are higher in colostrum than in mature milk (Scammell & Billakanti 2022). Colostrum is also richer in several essential minerals, including calcium, sodium, copper, selenium, iron, zinc, magnesium, manganese, and phosphorus (McGrath et al. 2016). The vitamins and minerals found in colostrum help in the metabolism of fats and proteins, have antioxidant properties, and aid in proper functioning of the nervous system (Buttar et al. 2017). Colostrum also contains multiple hormones, including growth hormone, prolactin, somatostatin, oxytocin, luteinizing hormone–releasing hormone, leptin, thyroid-stimulating hormone, thyroxine, calcitonin, estrogen, and progesterone. Increased gut permeability in the neonatal period allows these factors to enter the circulatory system to influence the developing calf (Lopez & Heinrichs 2022).

2.5. Cytokines and Immune Regulators

Cytokines are a diverse group of proteins, peptides, and glycoproteins secreted by T-helper cells and activated macrophages. Although present at minute concentrations in colostrum (10–1,000 pg/mL), cytokines show pro- or anti-inflammatory activity that supports immune activation and recruitment against pathogenic bacteria, viruses, and fungi (Playford & Weiser 2021). Cytokines in colostrum include interleukins (ILs), tumor necrosis factors (TNFs), and interferons. Several types and subtypes of cytokines and IL are present in colostrum, including IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, IFN-γ, TNF-α, and TNF-γ receptors (McGrath et al. 2016). Concentrations of IL-1β, IL-6, TNF-α, IFN-γ, and IL-1ra are higher in colostrum than in mature milk (McGrath et al. 2016). Colostrum also comprises maternal leukocytes, such as B and T lymphocytes, macrophages, and neutrophils (Playford & Weiser 2021). Leukocytes protect against enteric pathogens by directly acting on the microbe, in addition to stimulating a local immune response, such as the production of cytokines, IgG, and antimicrobial factors (Stelwagen et al. 2009). Unfortunately, commercial preparation techniques typically remove leukocytes from the final product. Colostrinin (or proline-rich polypeptide) is a polypeptide that helps regulate the production of cytokines and inhibits the production of damaging reactive oxygen species (Zabłocka et al. 2020). The amino acid compositions of colostrinin from ovine, bovine, and human colostrum are similar (Kruzel et al. 2001). Although not entirely chemically defined, colostrinin constitutes a mixture of at least 32 peptides with molecular weights ranging from 0.5 to 3 kDa (Rattray 2005). Colostrinin has been shown to prevent allergic inflammation due to common indoor and outdoor allergens in a murine allergic airway inflammation model, and immunocompromised rats infected with enterotoxigenic *E. coli* (ETEC) had reduced endotoxin levels and infected lymph nodes when treated with colostrinin (Boldogh et al. 2008). MicroRNAs (miRNAs) with immune-regulating potential are also present in colostrum (Sun et al. 2013). miRNAs are short, noncoding RNA molecules that can regulate gene expression at the post-transcriptional level, representing a possible method of postnatal signaling from the mother to the neonate (Van Hese et al. 2020). miRNAs are packaged in microvesicles, allowing stability during passage through the GI tract, and may influence lymphoid cell function within the intestine (Van Hese et al. 2020). Research in other species suggests that once absorbed by the neonate, miRNAs from colostrum may be important in the differentiation and functional development of the intestinal epithelium and the maturation of the neonate's immune system (Hatmal et al. 2022).

2.6. Growth Factors

Growth factors are polypeptides that stimulate cellular processes, including cell proliferation, migration, and differentiation (Gauthier et al. 2006). Insulin-like growth factor (IGF) is the most abundant growth factor in colostrum (Scammell & Billakanti 2022). IGF-I and IGF-II concentrations in colostrum range from 50 to 2,000 μg/L and 200 to 600 μg/L, respectively, whereas their concentration in mature milk is less than 10 μg/L (McGrath et al. 2016). IGF-I is an anabolic factor that enhances protein accumulation and mediates the growth-promoting action of growth hormone. Epidermal growth factors (EGFs) stimulate the proliferation of epithelial and epidermal cells, act as differentiation factors, and modulate hormone synthesis. The concentration of EGFs in colostrum varies from 4 to 320 μg/L and ranges from 2 to 155 μg/L in milk (Scammell & Billakanti 2022). Transforming growth factors (TGFs) maintain the equilibrium between cell proliferation and differentiation. TGF-α helps in reducing gastric acid production, increasing gastric mucus production, and stimulating gut growth and repair (Coffey et al. 1995). TGF-β acts as a chemoattractant for neutrophils and increases epithelial cell migration at the edges of wounds (Pakyari et al. 2013). Concentrations of TGF-β in colostrum are much higher (20–40 mg/L) than in milk (1–2 mg/L) (Playford & Weiser 2021). Vascular endothelial growth factor (VEGF) is a heparin-binding glycoprotein that stimulates proliferation and new vessel formation and vascular permeability-enhancing activity (Keck et al. 1989). Because of its angiogenic activity, the VEGF content of colostrum may have value in enhancing local vascular supply in conditions such as peptic ulceration (Playford & Weiser 2021). Milk-fat globule-epidermal growth factor 8 (MFG-E8) is a secreted protein, forming an integral component of milk-fat globules. MFG-E8 is present in colostrum in high concentrations and may influence the immune and repair response of the suckling neonate (Chatterton et al. 2013). MFG-E8 enhances the removal of damaged and apoptotic cells by phagocytosis, induction of VEGF-mediated new vessel formation, and enhancement of mucosal healing (Yi 2016).

2.7. Microbiome

The microbiome comprises the microbiota and its "theater of activity," encompassing the combined nucleic acids (including viruses and bacteriophages), structural components, and microbial metabolites related to the microbiota (Berg et al. 2020). Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria are the most abundant bacterial phyla in colostrum (Vasquez et al. 2022, Yeoman et al. 2018). The colostrum microbiota was found to share approximately 10.6% and 9.6% of operational taxonomic units with luminal and mucosal microbiota of the calves, respectively, suggesting colostrum contributes to the makeup of the calf GI tract microbiota in early life (Yeoman et al. 2018). Probiotics have been defined by the Food and Agriculture Organization and World Health Organization as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (FAO/WHO 2001, Hill et al. 2014). Colostrum contains various bacteria, including *Lacticaseibacillus casei*, *Lactiplantibacillus plantarum*, *Bifidobacterium pseudolongum*, and *Bacillus subtilis* (Vasquez et al. 2022, Yeoman et al. 2018). Colostrum is also a source of potentially pathogenic bacteria, including *Streptococcus uberis*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Staphylococcus aureus*, and *Corynebacterium* spp. (Derakhshani et al. 2018, Fasse et al. 2021). Pathogens originate from mammary gland infections and improper colostrum harvest, handling, and storage (Godden et al. 2019). Colostrum quality is typically evaluated by the IgG content; however, total bacterial count (TBC) should also be considered due to negative effects on passive transfer of immunity in calves and industrial processing (Cummins et al. 2017, Fasse et al. 2021). TBCs of less than 100,000 colony forming units (cfu)/mL and coliform counts of less than 10,000 cfu/mL are considered acceptable (Godden et al. 2019). Calves fed colostrum with low TBC have decreased pathogenic bacterial colonization and a higher prevalence of beneficial bacteria, including *Bifidobacterium* spp. and *Lactobacillus* spp. (Fischer et al. 2018, Malmuthuge et al. 2015). Recent human studies indicate that bacteriophages are transmitted from mother to infant via breastfeeding (Pannaraj et al. 2018); however, we are not aware of any studies that have investigated the presence of bacteriophages in bovine colostrum.

3. PRODUCTION OF BOVINE COLOSTRUM PRODUCTS

Bulk milk tank collections exclude colostrum for the first 4–5 days postpartum because the low clotting temperature and high protein content hamper industrial processes (Hesami et al. 2020). Farmers that supply colostrum manufacturers normally ship frozen colostrum to central processing facilities, where it is used to produce whole colostrum powders via conventional dairy processing methods. Manufacturers also use colostrum to isolate individual components, typically IgG and lactoferrin, through a combination of chromatography and tangential flow filtration steps, for addition to dietary products such as infant milk formula and calf dietary supplements (Scammell & Billakanti 2022). The United States, Canada, and India are the main producers of colostrum products due to their practice of year-round calving, which ensures a consistent supply of colostrum for processing (Scammell & Billakanti 2022). PanTheryx (Colorado, USA) is the leading supplier of colostrum products worldwide and recently received the generally recognized as safe classification from the US Food and Drug Administration (Sydney et al. 2022). Commercial products for both veterinary and human applications are typically in the form of capsules, lozenges, chewing gums, powder, or whole colostrum drinks. Whole colostrum has also been used as an additive in dairy products such as yogurt, kefir, fermented milk, ice cream, cheese, and butter to enhance their bioactive composition (Mehra et al. 2021). Traditional colostrum foods are also produced throughout the world, including khess (India), kalvdans (Scandinavia), abrystir (Iceland), råmelk (Norway), leipäjuusto (Finland), molozyvo (Ukraine), and groosniuys (Isle of Man) (Mehra et al. 2021). Elimination of bacterial contamination and preservation of bioactive components are the primary challenges of generating colostrum products (Kaplan et al. 2021). Preservation and processing methods used to produce colostrum products for supplementation in animal and human studies are discussed in the following section.

3.1. Refrigeration and Freezing

Up to 90% of Irish and US dairy producers freeze colostrum for on-farm and industrial usage (Cummins et al. 2016a, Usuga et al. 2022). Frozen colostrum is typically used to create a colostrum bank for newborn calves that cannot be fed their mothers' colostrum immediately after birth (Lopez & Heinrichs 2022). Freezing is the optimal preservation method for colostrum and storage for up to 1 year leads to no significant alterations in the bioactive composition (Godden et al. 2019). Thawing by the au bain-marie method with temperatures <40°C has been shown to have no effect on composition (Robbers et al. 2021). However, TBC and pH are significantly altered when colostrum is stored at >4°C (Cummins et al. 2016b). Gross increases in TBC and pH occur in the first 6 hours postpartum; therefore, rapid storage at ≤4°C is essential (Cummins et al. 2016b). Storage at ≤4°C for 2 days also sufficiently minimizes bacterial growth to levels suitable for processing and ensures passive transfer to calves occurs (Cummins et al. 2017).

3.2. Thermal Treatment

Pasteurization is a heat treatment process used to reduce the total number of microorganisms and minimize the number of pathogens in colostrum (Robbers et al. 2021). High-temperature short-time (HTST) pasteurization at 72°C for 15 seconds and low-temperature long-time (LTLT) pasteurization at 60°C for 30 minutes are the two most common pasteurization methods employed in producing colostrum products (Jay 1998). The bioactive components in colostrum are heat labile; for instance, immunoglobulins unfold above 65°C and denature at 89°C and other significant bioactives denature between 62°C and 78°C (Indyk et al. 2008). HTST is efficient at pathogen elimination in colostrum but results in a significant loss of bioactives and increases viscosity, thus affecting downstream processing (Elsohaby et al. 2018). LTLT at 60°C for 30 or 60 minutes is the optimal pasteurization method for colostrum for the reduction of microbial contamination and maintenance of bioactive components (Mann et al. 2020).

3.3. Drying

Drying colostrum to a powder form reduces the water activity (aw) to an aw below 0.2 and slows microbiological, chemical, and enzymatic activity, allowing for long storage periods without activity loss of bioactive components (Guiné 2018). Spray drying refers to the conversion of a liquid feed to powder by spraying into a hot dryer to rapidly remove moisture (Kandasamy & Naveen 2022). Freeze drying or lyophilization refers to the elimination of moisture from frozen food molecules through sublimation (Kandasamy & Naveen 2022). The thermo-labile nature of colostrum requires the omission of conventional pasteurization of colostrum prior to spray drying; hence, spray-dried powder may contain pathogens and spoilage microorganisms (Borad et al. 2019). For instance, potentially harmful *Bacillus* species were detected in spray-dried colostrum powder sold in the US market (Hayes et al. 2012). Freeze drying is significantly more effective at preserving bioactive constituents than spray drying (Chatterton et al. 2020). However, high production costs, longer processing time, and problems in scaling up freeze drying have limited its industrial application for the manufacture of colostrum products. Therefore, spray drying is the most common drying method for colostrum (Chelack et al. 1993). Electrostatic spray drying is the newest drying technology aimed at heat-sensitive materials and has the potential to reduce denaturation of heat-labile components in colostrum (Ackerman et al. 2019).

3.4. Emerging Processing Methods

Because of the thermal instability of bioactive constituents in colostrum, numerous nonthermal technologies have been explored for the production of colostrum products. Anaerobic fermentation, termed bovine colostrum silage (BCS), is produced by storage at mild temperatures (17–22.5°C) for a minimum period of 35 days (Kraus et al. 2021). BCS can be stored for 2 years, is low cost, does not require refrigeration, freezing, or use of additives, and can be used for feeding calves (Halavach et al. 2022). *Streptococcus lactis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, and *L. plantarum* have been used to produce BCS (Halavach et al. 2022). High-pressure processing (HPP) exposes foodstuffs to elevated pressures (100–1,000 MPa) to achieve microbial destruction without affecting low-molecular-weight compounds (Li et al. 2006). HPP at 300–400 MPa for 30 minutes has been shown to effectively reduce TBC while maintaining IgG concentrations in colostrum (Foster et al. 2016). Irradiation utilizes ultraviolet light to inactivate microorganisms in food materials (Cutler & Zimmerman 2011). A negative linear relationship between duration of continuous ultraviolet light treatment and the concentration of IgG and bacterial contaminants has been reported (Pereira et al. 2014). Membrane processing, pulsed electric field, nanoencapsulation, and liposomal technologies are emerging food processing techniques warranting further investigation for the production of colostrum products (Borad & Singh 2022, Kaplan et al. 2021).

4. HUMAN HEALTH APPLICATIONS OF BOVINE COLOSTRUM

Prior to the advent of antibiotics, bovine colostrum was consumed by humans for thousands of years for its antibacterial properties. For example, as part of Ayurveda, the ancient system of medical practice in India, colostrum was used in the treatment of eye infections (Buttar et al. 2017). At present, there are more than 120 clinical trials taking place worldwide investigating the use of colostrum in human health promotion and the amelioration of numerous disease states in adults and neonates (see **https://trialbulletin.com/lib/trials/term=Colostrum**). This section discusses recent preclinical and clinical studies of colostrum supplementation for human health applications. **Table 2** outlines a more detailed description of a selection of clinical trials of colostrum supplementation in humans.

4.1. Infant Health

In vitro studies have shown that fortification of human milk with bovine colostrum increases its antibacterial activity (Gao et al. 2021). Furthermore, in vitro studies have reported that colostrum-derived IgG fractions have prebiotic effects, as they are capable of increasing the adhesion of *Bifidobacterium* spp. and *Lactobacillus* spp., important early colonizers of the infant gut, to human intestinal cells (Morrin et al. 2019, 2020). Stepwise pilot-phase safety trials of colostrum supplementation in preterm infants (<37 weeks gestation in humans) have shown a shortened time to reach full enteral feeding (when feeding with infant formula), no adverse clinical effects, and/or increased enteral protein intake (when feeding with human milk) (Juhl et al. 2018, Li et al. 2017). A larger clinical trial is currently taking place to investigate the use of bovine colostrum as a fortifier to human milk in preterm infants ($n = 350$) (see **https://clinicaltrials.gov/ct2/show/NCT03085277**). Necrotizing enterocolitis (NEC) is the leading cause of death from GI disease in infants, affecting 3–10% of hospitalized preterm infants worldwide (Burrin et al. 2020).

Table 2 A selection of human clinical trials studying the effects of supplementation of whole bovine colostrum or isolated compounds in human health promotion

Application	Studied sample	Colostrum form and intervention	Benefits	Reference
NEC	80 preterm neonates	Immuguard® (Dulex-Lab Pharmaceutical Co.); 20 mL/kg/day for first 2 weeks of life	Decrease of feeding intolerance, NEC, late-onset sepsis, and mortality	Ismail et al. 2021
Exercise-induced immune dysfunction	31 male athletes	Powdered whole colostrum; 20 g per day for 58 days	Prevention of prolonged exercise-induced immunodepression	Jones et al. 2019
Rotavirus and *Escherichia coli* infection-related acute diarrhea	160 children, ages 6 months to 2 years old	3 g BC powder diluted in 50 mL water, daily, orally, 1 week	Reduction of frequency and duration of vomit and diarrhea episodes	Barakat et al. 2020
Drug-induced lesions	62 children, ages 1–18 years old	Spray-dried BC powder (Biofiber-Damino™), 7.5–30 g/day, 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	Rathe et al. 2020
Enterotoxigenic *E. coli* 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 diarrhea Reduction of abdominal pain complaints No effect on the viability of the challenge strains	Otto et al. 2011
Dietary supplement for preterm infants	40 preterm infants	Powered colostrum product, ColoDan (Biofiber-Damino™, Gesten, Denmark) as a supplement to mother's own milk	Colostrum feeding showed no adverse clinical effects, increased enteral protein intake (when feeding with human milk), and/or a shortened time to reach full enteral feeding (when feeding with infant formula)	Juhl et al. 2018

Abbreviations: BC, bovine colostrum; HBC, hyperimmune bovine colostrum; NEC, necrotizing enterocolitis.

Although encouraging results have been seen in animal models, human studies have so far not shown a significant benefit of colostrum products in reducing the incidence of or mortality from NEC in preterm infants; however, gut priming effects have been reported (Ismail et al. 2021, Sharma et al. 2020, Tao et al. 2020).

4.2. Sport and Exercise Nutrition

Colostrum has attracted significant interest within sports nutrition to influence body composition, physical performance, recovery, immune function, illness risk, and gut damage and permeability in athletes (Davison 2021). The World Anti-Doping Agency previously advised athletes against taking colostrum for fear of causing a rise in circulatory levels of IGF-I, resulting in doping penalties, but this has since been proved false (Davison et al. 2019). Colostrum supplementation has been shown to ameliorate several performance decrements caused by periods of high-intensity, intermittent, and endurance performance (Kotsis et al. 2018). Daily colostrum supplementation for 2–12 weeks has been reported to have beneficial effects on clinically relevant immune functions and the risk of suffering upper respiratory tract infections or symptoms in athletes (Jones et al. 2016, 2019). Numerous studies have reported benefits of colostrum supplementation on gut permeability, especially during periods of intensified training (March et al. 2017, 2019). However, null effects on GI permeability or damage markers in athletes have also been reported (McKenna et al. 2017, Morrison et al. 2014). The balance of available evidence for gut permeability and illness risk is positive, but further research is required to fully determine all mechanisms responsible for these effects in athletic populations (Davison 2021).

4.3. Skincare

Colostrum and its components have been investigated for their usage in skincare products (Sydney et al. 2022). In vitro studies have demonstrated that colostrum induces proliferation and differentiation of skin cells and stimulates repair and reduces artificially induced inflammation in animal models (Hong & Park 2014, Kovacs et al. 2020). More recently, combining colostrum with honey reduced scars and exudates, provided pain relief, protected against infection, and stimulated the growth of granulation tissue in rat models of cutaneous wound injuries (Tanideh et al. 2017). In human volunteers, topical administration of colostrum-derived lactoferrin reduced inflammation after exposure to skin allergens (Griffiths et al. 2001).

4.4. Respiratory Tract Infections

Human respiratory syncytial virus (RSV) is a common, contagious virus that causes respiratory infections, namely bronchiolitis, the common cold, and serious illness for infants and elderly persons (Nederend et al. 2020). Intranasal administration of colostrum-derived IgG prevented and neutralized RSV infections in mice (Nederend et al. 2020). Immunization of pregnant cows with the S1 receptor-binding domain protein and trimeric S protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recently used to develop SARS-CoV-2-specific neutralizing antibodies, which demonstrated blocking of the interaction between the trimeric S protein and angiotensin-converting enzyme 2 (ACE2) (Kangro et al. 2021). This study led to the formulation of a nasal spray, BioBlock, which is currently being investigated in a clinical trial (Uusküla et al. 2022).

4.5. Diarrhea

Colostrum has proved to be an effective adjuvant therapy for both viral and bacterial diarrhea in children and adults. A meta-analysis of five randomized control trials in children ($n = 324$) reported that colostrum supplementation significantly reduced stool frequency and occurrence of diarrhea caused by rotavirus or *E. coli* (Li et al. 2019). Colostrum supplementation in a randomized control trial in adult patients ($n = 42$) with HIV-related diarrhea resulted in reduced stool frequency and fatigue and permitted weight gain compared to routine care alone (Kaducu et al. 2011). In adults, a randomized control trial ($n = 90$) showed colostrum supplementation was significantly effective at protecting against travelers' diarrhea caused by ETEC (Otto et al. 2011). The product used in the aforementioned study, TRAVELAN® (600 mg/day anti-*E. coli*/antidiarrheal HBC) is currently sold in several countries (Otto et al. 2011).

4.6. Drug-Induced Gut Injuries

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs worldwide for the treatment of pain; however, they can cause gastric and intestinal damage such as peptic ulceration and injury to both the small and large intestine (Arslan et al. 2021). Colostrum protected against indomethacin-induced mucosal damage and increased villus height in vivo (mice and rats) and in vitro (HT-29 cells) (Playford et al. 2020, Yamamoto et al. 2013). Colostrum feeding decreased intestinal permeability and intestinal villi harm in rats with diclofenac-induced mucosal damage (Kim et al. 2005). Intestinal damage caused by chemotherapy treatment in pigs showed that colostrum supplementation reduced inflammatory markers and increased intestinal enzyme activity, resulting in reduced intestinal drug toxicity (Pontoppidan et al. 2015). Randomized crossover trials of indomethacin-induced intestinal permeability in humans indicate that colostrum supplementation protects against NSAID injury (Playford et al. 2001). Mechanistically, the beneficial effects of colostrum on NSAID injuries have been attributed to the affinity of the C-terminal half of lactoferrin (C-lobe) for NSAIDs (Mir et al. 2009).

4.7. Short Bowel Syndrome

Short bowel syndrome (SBS) is an intestinal insufficiency resulting from intestine resection due to infarction of the mesenteric vessels, trauma, abnormalities, or complications of Crohn's disease. Promising results from animal models of SBS suggest that the supplementation of diets with colostrum led to weight gain and significant improvements in intestinal functioning (Aunsholt et al. 2018). Clinical trials in children and adults have not shown that colostrum provides significant improvements to SBS clinical markers (Aunsholt et al. 2014). Despite encouraging results from animal studies, the requirement for invasive sampling for endpoint measurements of SBS has limited studies on the effects of colostrum supplementation on SBS in humans.

4.8. Inflammatory Bowel Disease (IBD)

Colostrum and its constituents have shown promising results in the treatment of inflammatory bowel disease (IBD), a group of diseases that affect the intestine, classified by two main phenotypes: ulcerative colitis and Crohn's disease (Sienkiewicz et al. 2021). In mouse models of chemically induced colitis, colostrum feeding was shown to prevent and reduce colitis (Filipescu et al. 2018, Spalinger et al. 2019). A recent study reported that colostrum supplementation in mice with colitis led to a reduction in inflammatory markers of colitis and stimulation in the growth of *Bifidobacterium* spp. and *Lactobacillus* spp. (Menchetti et al. 2020). In humans, colostrum was shown to improve the symptoms and histological scores of patients with distal colitis who received colostrum enemas in addition to mesalazine, a medication routinely used to treat IBD, compared to controls who only received mesalazine (Khan et al. 2002).

5. VETERINARY APPLICATIONS OF BOVINE COLOSTRUM

Bovine colostrum is commonly used as a nutritional supplement and alternative source of passive immunity in domestic animals and pets. Furthermore, colostrum has been investigated in production animals to improve growth performance parameters such as body weight gain, feed intake, and feed conversion ratio. This section discusses studies of colostrum supplementation for veterinary applications.

5.1. Bovines

Failed passive transfer of immunity is a common issue for bovines (Lopez & Heinrichs 2022). Colostrum replacers (>100 g IgG per dose) in the form of dried powders are a viable alternative when maternal colostrum is unavailable or of poor quality for feeding (Godden et al. 2019). The ease of storage and preparation of colostrum replacers is particularly advantageous over thawing maternal colostrum from a colostrum bank (Lago et al. 2018). However, replacement products should not replace high-quality colostrum, as they typically lack antigen-specific antibodies against farm-specific pathogens (Cabral et al. 2013). Colostrum supplements (<100 g IgG per dose) are commonly used in conjunction with maternal colostrum to ensure passive immune transfer occurs (Godden et al. 2019).

5.2. Pigs

Pigs represent the most widespread use of colostrum in nonbovines. Modern pig breeds often produce more offspring than the number of functional teats on sows; thus, bovine colostrum has been explored as an alternate source of passive immunization for newborn piglets (Kirkden et al. 2013). Studies in preterm piglets, a model for preterm human infants, have shown that bovine colostrum is equally as effective as porcine colostrum at improving digestive and absorptive functions, inducing body and gut growth, dampening inflammation, protecting against NEC and late-onset sepsis, and improving systemic immunity relative to formula feeding (Yan et al. 2021). Furthermore, colostrum-fed preterm piglets display an exceptional capacity to rapidly adapt their gut and immune development to that in term pigs (within 1 to 2 weeks) (Rasmussen et al. 2016). As a basis for human trials, colostrum has been explored as a fortifier to donor human milk in preterm pigs in the first weeks of life. Fortification of donor human milk with colostrum was superior to formula-based fortifiers to support growth, gut function, nutrient absorption, mucosal defense, and reduction in the density of mucosa-associated bacteria and putative pathogens (Sun et al. 2019). It has been suggested that the growth-stimulating effect of adding colostrum to human milk or formula may relate to indirect effects via the developing gut microbiota, potentially via immunoglobulins, which, in turn, increase or decrease plasma amino acid levels so that the environment is more favorable to microbial growth (Jiang et al. 2022). Future studies are needed to investigate the ability of colostrum to regenerate a gut first exposed to a period of formula feeding (Brunse et al. 2019).

5.3. Poultry

Colostrum has been used as a feed additive in poultry production to maximize protein quality and growth performance and decrease feed costs (Mehra et al. 2022, Playford & Weiser 2021). Studies have reported that supplementing the diet of broiler chickens with 2–5% colostrum/kg improved feed conversion efficiency, increased body weight, and reduced mortality rates compared to control diet groups (Afzal et al. 2017). In young broiler chickens (1–10 days old) under heat stress, colostrum feeding increased thigh and breast size (Parapary et al. 2020).

5.4. Fish

Colostrum and its constituents have shown encouraging results as a feed supplement in fish. Colostrum feeding to *Piaractus mesopotamicus* thickened muscle layers of the intestinal epithelium and increased nutrient absorption concentration of goblet cells and superoxide dismutase activity in the gut, indicating a protective effect on enteric cell protection (Moretti et al. 2019). Colostrum feeding also increased goblet cell concentrations in the enteric mucosa of *Salminus brasiliensis* (da Cruz et al. 2016, Nordi et al. 2016). Supplementation of bovine lactoferrin was shown to suppress the stress responses in Siberian sturgeon (Falahatkar et al. 2014). Bovine lactoferrin supplementation also enhanced immune function and disease resistance in Pacu and Dorado species (Machado-Neto et al. 2016).

5.5. Goats

Numerous authors have reported that colostrum products are an effective alternative to goat colostrum in newborn goat kids. Feeding bovine colostrum to newborn goat kids resulted in no difference in the enteric histology and histomorphometric features of the GI tract compared to feeding goat colostrum (Nordi et al. 2013). Interestingly, one study reported that the number of sialomucins, which have cytoprotective and antiadhesive effects, was higher in the jejunum epithelium of goat kids fed with lyophilized colostrum than in goat kids fed with goat colostrum (Machado-Neto et al. 2013).

5.6. Dogs

Several canine nutritional supplements and colostrum-based powdered dog foods are available (Beynen 2020). Recently, weaned puppies fed diets supplemented with bovine colostrum demonstrated improved fecal scores when placed in a new environment that favored stress-related diarrhea (Giffard et al. 2004). Colostrum supplementation to 2–7-year-old huskies for 40 weeks increased fecal IgA levels compared to controls, suggesting enhanced gut-associated lymph tissue function (Satyaraj et al. 2013). Furthermore, these subjects responded to canine distemper virus (CDV) vaccination with higher plasma levels of anti-CDV IgG and had increased fecal microbiota diversity, suggesting positive effects on immune function and gut microbiome (Satyaraj et al. 2013). More recently, a pilot crossover trial in which male beagles were supplemented with 1 g of bovine colostrum per day for three weeks, in addition to a set of four probiotic strains at 2.9×10^9 cfu, was associated with improvements in protein digestibility (Dequenne et al. 2014).

5.7. Cats

Kittens fed a diet containing 0.1% spray-dried bovine colostrum during the weaning period were shown to have increased fecal IgA expression and a faster and stronger antibody response to a rabies vaccine booster, indicative of better localized and systemic immune function, respectively (Gore et al. 2021). Supplementation also helped to maintain intestinal microbiota stability in kittens (Gore et al. 2021). These results show that colostrum supplementation can help strengthen the immune system and enhance the gut microbiota stability of growing kittens.

5.8. Horses

Colostrum has been explored to improve the immunological health and athletic performance of horses. Colostrum has been shown to be a suitable alternative for the transfer of passive immunity in foals (Holmes & Lunn 1991). A bovine colostrum-based supplement was shown to significantly reduce the duration of respiratory disease in thoroughbred yearlings (Fenger et al. 2016). In addition, in a randomized crossover trial of racing thoroughbreds, colostrum supplementation led to better race performances and quicker returns to racing compared with controls (Fenger et al. 2014b). Colostrum supplementation in racehorses does not increase serum IGF-I concentrations; therefore, there are no regulatory concerns over its utilization for athletic performance (Fenger et al. 2014a).

6. FUTURE CHALLENGES

Milk is already among the most versatile products in the food industry. World milk production was recorded at 823 million tons in 2017 and is expected to increase by 22% by 2027 (Organ. Econ. Co-op. Dev. 2018). This growing supply chain means that there will be more access to bovine colostrum for product manufacture. However, there are several issues to address in the manufacture of colostrum products to maximize its benefits for use in veterinary and human health.

6.1. Quality Control of Products

To interpret results from clinical trials accurately, especially when comparing results from different investigators, the colostrum products being used need appropriate quality control. The quality of commercial colostrum products is usually accepted as involving the total protein and immunoglobulin concentrations with no specification to either individual growth factor concentrations or, of more value, total growth factor bioactivity. A recent study highlighted the severity of this issue, reporting up to sixfold differences in the bioactivity of 20 different commercial colostrum products (Playford et al. 2020). These wide variations in bioactivity are of particular concern if colostrum is being used as a therapeutic agent for a medical condition, where consistency of the product is vital. Encouragingly, products that displayed high levels of bioactivity in this study had previously been shown to exert beneficial effects for numerous health applications (Playford et al. 2020). If the bioactivity level of products was noted by researchers in their publications, it would be possible to determine dose-response profiles and establish the minimum efficacious dose of colostrum products.

6.2. Scaling Up of Polyclonal Antibody Production

Colostrum-derived polyclonal antibodies targeting pathogens, immune modulators, or cancerous cells continue to show promise, but to date this approach has been overtaken by the rapid development and cost reductions of monoclonal antibodies that have reshaped parts of the pharmaceutical industry. Bovine polyclonal antibodies have advantages, particularly considering direct targeting of disease in the lumen of the gut, but the developmental pathway, good manufacturing practices for repeatable potency, preclinical and clinical trials, and final regulatory approval remain challenging.

6.3. Measurement of Bioactive Constituents

At present, radial immunodiffusion (RID) is considered the gold standard for IgG detection but is slow and costly and cannot be performed in the field (Godden et al. 2019). On-farm detection methods, such as refractometry, indirectly measure IgG and often overestimate actual concentrations (Godden et al. 2019). As the composition of bovine colostrum is widely variable between individual cows, the development of rapid and accurate on-farm methods for the determination of colostrum quality will aid in the production and standardization of high-quality colostrum products. One such example includes the recently developed split trehalase IgG quantification assay, which is comparable to RID testing and is compatible with on-farm application (Drikic et al. 2018).

7. CONCLUSIONS AND FUTURE PERSPECTIVES

Bovine colostrum harbors a diverse array of bioactive components suitable for the development of functional foods, nutraceuticals, and pharmaceuticals with veterinary and human health applications. Increases in worldwide milk production and improving processing techniques indicate there is significant potential for expansion and growth in the colostrum-based products market. Studies in humans and animals have indicated benefits of colostrum-based products in the amelioration of disease states pertaining to all stages of life. At present, bovine colostrum is marketed as a health-food supplement and has better evidence across a wider range of applications than many of its competitors. However, colostrum products need to overcome several obstacles before consideration as pharmaceutical products. Stricter quality control, using methods such as bioassays, is imperative to accurately compare and interpret results from human clinical trials. Such assays would elucidate the dose-response effects in clinical settings, which is the norm for pharmaceutical products. Further studies are required to determine the effective dosages of colostrum products to elicit beneficial effects. Better-conducted clinical randomized control trials of colostrum supplementation are required, as systematic reviews of colostrum to date have been severely hampered by heterogeneous and poor-quality studies. Finally, more studies elucidating the mechanisms behind the beneficial effects of colostrum supplementation are needed.

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