Review

Bovine Colostrum for Human Consumption - Improving Microbial Quality and Maintaining Bioactive Characteristics through Processing

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Abstract: The main purpose of bovine colostrum, being the milk secreted by a cow after giving birth, is to transfer passive immunity to the calf. The calves have an immature immune system as they lack immunoglobulins (Igs). Subsequently, the supply of good quality bovine colostrum is required. The quality of colostrum is classified by low bacterial counts and adequate Ig concentrations. Bacterial contamination can contain a variety of human pathogens or high counts of spoilage bacteria, which becomes more challenging with emerging use of bovine colostrum as food and food supplements. There is also a growing risk for the spread of zoonotic diseases originating from bovines. For this reason, processing based on heat treatment or other feasible techniques are required. This review provides an overview of literature on the microbial quality of bovine colostrum and processing methods to improve its microbial quality and keep its nutritional values as food. The highlights of this review are: high quality colostrum is a valuable raw material in food products and supplements, the microbial safety of bovine colostrum is increased using appropriate processing-suitable effective heat treatment, which does not destroy the high nutrition value of colostrum, the heat treatment processes are cost-effective compared to other methods, and heat treatment can be performed in both small- and large-scale production.

Keywords: bovine colostrum; bacteria; pathogens; probiotic bacteria; cost-effective processing; heat treatment; pasteurization; contamination control; immunoglobulins; enzymes

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1. Background on Bovine Colostrum, Contaminants and Processing

Bovine colostrum is the first milk given by a cow after parturition as nutrition to the newborn calf. This liquid is essential for conferring of passive immunity to the newborn calves. The newborn calf lack immunization at birth and require the uptake of immunoglobulins (Igs) within 24-36 hours after birth. Initial milk is considered bovine colostrum up to 3 days postpartum. Especially, an elevated concentration of immunoglobulin G (IgG) is characteristic for bovine colostrum, as it is of significance in the transfer of passive immunity [1]. Besides these Igs there are other immune components present, e.g. enzymes or lactoferrrin (LF), which act as nonspecific antibacterial factors [2]. Furthermore, healthy cows produce colostrum in excess of the calf's need, which means that ethical asepects for calves are not impacted [3]. Therefore, there is an increasing interest for human use of bovine colostrum as a neutraceutical food [4]. Several human studies provide information on treatment or prevention effectiveness in bone development, respiratory, inflammatory and gastrointestinal diseases as e.g. inflammatory bowel syndrome and *Escherichia coli* induced diarrhea [5-7]. Additionally, improvements in athletes' performance has been confirmed [8].

1.1. Contamination

The microbiology in raw colostrum is expected to be highly diverse. There are risks for the growth of both spoilage and pathogenic bacteria. Therefore, the consumption of raw contaminated colostrum may lead to illnesses in the calves due to spoiled nutrition and to intoxication or infections of *Staphylococcus* spp., *Bacillus* spp. or *Salmonella* spp. etc. in humans [9-10]. Especially well described is the occurrence of infectious bovine diseases e.g. mastitis. When the calves do not get enough good quality colostrum, the calves can develop microbial diseases due to inadequate passive immunity [11-13]. Specific microbes, e.g. *Mycoplasma bovis* or *Staphylococcus aureus,* in the colostrum provoke the mastitis [14].

The microbes in bovine colostrum have been reported in several papers and they mainly belong to the phyla Firmicutes, Proteobacteria, Bacteroides and Actinobacteria [14-16]. The harvesting procedure of bovine colostrum is a critical control point, when occurrence of contamination is to be reduced [15, 17].

1.2. Processing

Raw dairy products as bovine colostrum can be contaminated by several human pathogens during harvesting, which means that there is a need for treatment before consumption [18]. The processing techniques for an efficient inactivation of pathogenic/spoilage bacteria must be applied to obtain health promoting colostrum of good quality. The regulations for marketing dairy products require heat treatment or an equivalently effective treatment to improve the shelf life before selling the product [19]. The design of a heat treatment process for bovine colostrum will be introduced in this review. However, besides a mandatory efficient reduction of the bacterial count, the beneficial constituents in colostrum have to be preserved, not diminished, through the processing. Bioactive components, e.g. Igs, with nutraceutical value for humans are degrading through high temperature heat treatment of the colostrum [4, 20], which means that other feasible methods for the bacterial reduction are of interest to the industry. This review article focuses on specific nutritional values, microbial characteristics and basic heat treatment of bovine colostrum to improve its microbial quality and use for human consumption. Examples of food products manufactured from colostrum are given in the chapter “Products of Bovine Colostrum”.

2. Bioactive Components in Colostrum

2.1. Bioactive Compounds

The bioactive compounds in bovine colostrum play a key role in its high nutritional value for human consumers. The list of components with immunomodulatory capabilities comprises direct and indirect powerful mechanisms as well as adaption of the host’s immune response [21-22]. The worldwide market of colostrum has continuously increased between 2014 and 2020 with an estimated value of 3.046 billion US$ and it is expected that the market will increase further [23-24]. Predictions indicate an increase by 6.4 % per year between 2020 and 2030 on the global market, which can be explained by a rising request for health promoting foods, linked to emerging illnesses and health risks due to improper nutrition [24].

Colostrum and milk contain a variety of nutritious components with chemical/functional activities. The list of these bioactive compounds consists of carbohydrates, proteins, growth factors, cytokines, lipids, enzymes, vitamins and minerals [22]. Bioactive compounds are molecules needing activation through chemical reactions to perform specific functions. The bioactive components in bovine colostrum (Figure1) promote health [2, 25].

The amount of bioactive compounds in bovine colostrum is significantly higher than in milk [1]. This is proven by an elevated protein concentration, which is 15.9 g/100g within 24 h postpartum and 3.3 g/100g after 5 months [26]. 70-80% of this total protein content in colostrum are Igs, prevalent in concentrations of 30-200 g/L. The Ig concentration is declining soon after parturition, being considerably lower in milk with 0.4-1 g/L [1, 5]. The subcategory IgG1 accounts for 75% of the antibody content in colostrum, followed by IgM, IgA and IgG2 [27]. Morrill et al. [11] report that the average IgG concentration is dependent on number of parities of the cow, additional to duration of dry period and breed of the cow [28-29].

Saad et al. [30] have reported that colostrum has both antimicrobial and endotoxin-neutralizing effects. Thus, it can be effective in the prophylaxis of recurrent upper respiratory tract infections and diarrhea [30-31]. The consumption of bovine colostrum can also lead to changes in the respiratory microbiome, which was shown by nasal swab samples [31].

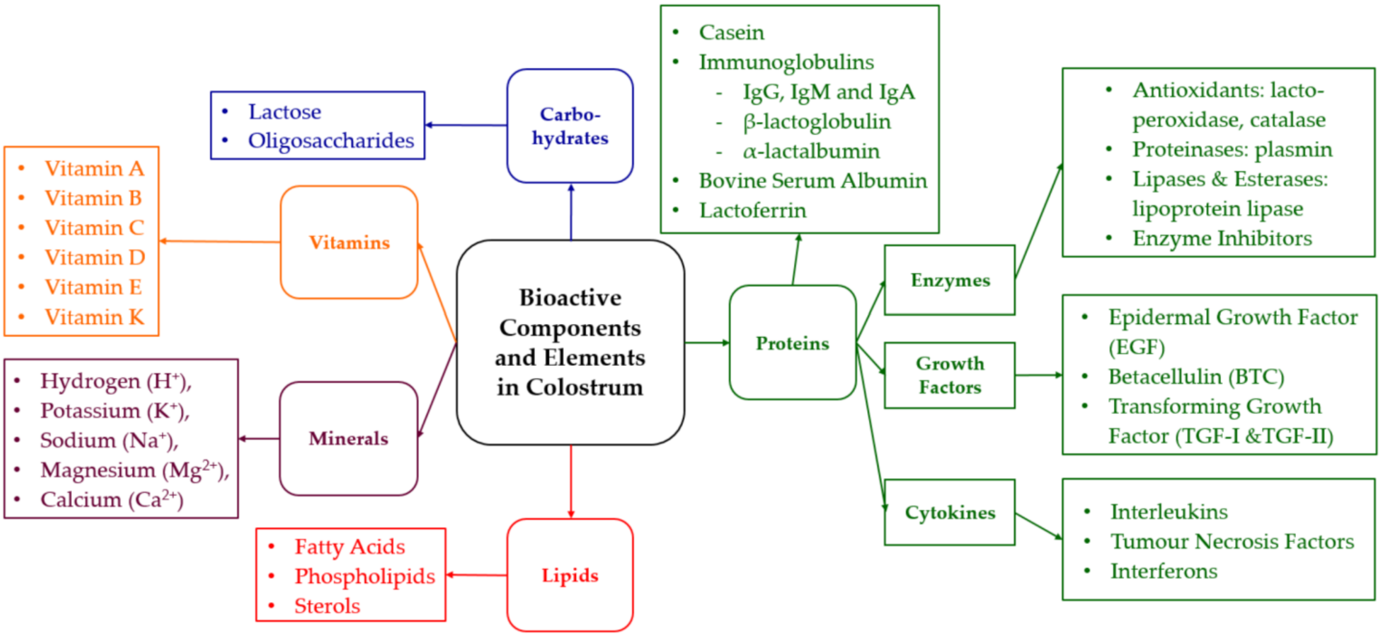

Figure 1. Overview of bioactive components and elements in bovine colostrum based on McGrath et al. [1] and Korhonen [2, 25]. The colors are differentiating various groups of constituents.

2.2. Immunoglobulins

Bovine colostrum contains a variety of different immunoglobulin-based antibodies (IgG1, IgM, IgA and IgG2). They are divided into the subcategories according to their mode of presence, i.e. monomeric as IgG and IgA, dimeric as IgA or pentameric as IgM, while the antimicrobial effects are initiated [27, 32]. General operating mechanisms of Igs comprise the prevention of microbes' surface-adhesion, inhibition of the bacterial metabolism, agglutination of bacteria and furthermore neutralising toxins and viruses. These mechanisms are performed by IgM antibodies in high efficiency. IgG, which is present in highest amounts, has versatile functioning mechanisms, it can activate complement-mediated bacteriolytic reactions or induce opsonisation by amplification of phagocytosis of bacteria by leucocytes. It has additionally been reported that bovine colostrum IgG can retain biological functionality with human digestion. After colostrum consumption, immunological activity in the ileum effluents of adults was discovered [27, 33]. Therefore, ingesting of these colostrum derived IgG can prevent both respiratory and gastrointestinal infections, which is enhanced through improved barrier integrity. By the prevention of respiratory infections, the development of allergies as e.g. allergic asthma can be prevented [34-35].

2.3. Enzymes

According to Fox and Kelly [36-37] about 70 indigenous enzymes have been identified in bovine milk. Both ribonucleases and lysozyme [EC 3.2.1.17] (LZM) are present in higher concentrations in colostrum than in milk with an extensively elevated concentration of enzymes in the early postpartum period [1, 37-38]. Enzymes have several purposes, e.g. they work synergic with other proteins to fulfil antimicrobial activities. LZM supports the digestive system or catalyzes other important reactions [2, 39].

The LZM plays an undoubtable substantial role in the body's immune system. It provokes bacteriolysis and opsonization having a general higher immune response as well as antiviral and antineoplastic activities [40]. This bacteriostatic effect inhibits the growth of bacteria and shows indirect bactericidal effects potentially effective against udder pathogens [38]. The LZM is effective through exhibiting lytic properties or by complementing the bactericidal action of antibodies [40]. Lie et al. [40] reported LZM activity in colostrum of 0.28 µg/mL on average, which is higher than in milk [39]. The peptidoglycan layer in the bacterial cell walls functions as the substrate for LZM. LZM is hydrolyzing the β (1→4)-bond between muramic acid and N-acetylglucosamine in the cell wall [37], which leads to lysis of bacterial cells [38]. As an example, LZM is effective against *E. coli* and *Pseudomonas aeruginosa* [41].

2.4. Lactoperoxidase

Lactoperoxidase [EC 1.11.1.7] (LPO) is the most common enzyme in milk and one of the major antimicrobial agents in colostrum [38, 42]. It was the first enzyme identified in milk in 1881 [36]. It has a broad substrate specificity [42]. The bactericidal mechanism of LPO requires the presence of low levels of hydrogen peroxide and thiocyanate anions. Antimicrobial active short-lived oxidation products e.g. hypothiocyanites are generated this way. This inhibits bacterial metabolism based on oxidizing essential sulfhydryl groups in proteins [38]. LPO is relatively heat-resistant and effective against different microbes [42].

The enzyme is produced in the mammary gland [36], where the epithelial cells gene is expressed encoding for LPO. It is also protecting the gland from infections, e.g. caused by pathogenic *Streptococcus* spp., *Listeria monocytogenes* or *P. aeruginosa* [38]. Meanwhile, LZM makes up 1.25-2.5% of the LPO activity [39]. Korhonen [39] reported an average LPO activity of 37.8 µg/mL. Neither LPO nor LZM accumulates during the dry period. These agents are produced after calving [39].

2.5. Non-enzymatic Bioactive Components

Lactoferrin (LF), being an iron-binding glycoprotein, is categorized as a multifunctional compound [42]. Both LF and transferrin make iron unavailable for bacteria and prevent bacterial multiplication [43]. LF is also reported to have proteolytic enzymatic activities [44]. LF inhibits the growth of both *E. coli* and *L. monocytogenes*. The mechanism presumably relies on the iron-binding capacity depriving the bacteria of their access to essential iron. The presence of LF enhances the antimicrobial effects of LZM [38]. It also exhibits synergistic effects in combination with LPO and Igs [45].

Both LF and LPO are produced in the mammary gland [39]. The biological activities of LF comprise antimicrobial, anti-oxidative, anti-inflammatory and anti-carcinogenic as well as immune response properties [42]. It is known to play a key role in the body's inert immune response and simultaneously to increase the susceptibility of bacteria to certain antibiotics, e.g. vancomycin, penicillin and cephalosporin [25]. Due to the beneficial health effects, bovine LF is getting attention for being used in functional foods [42]. Bovine LF has also inhibited growth of lung cancer cells in transgenic mice. Therefore, it could be applied as therapeutic agent against tumorigenesis with suppressing the inflammation of lung cells [46]. In a study by Kehoe et al. [47], the analysis of 55 colostrum samples revealed an average concentration of LF of 0.82 g/L. In comparison to milk with 0.1 g/L the concentration of LF is considerably higher in colostrum [45].

Another protein-based ingredient of bovine colostrum is casein, which occurs in higher concentrations postpartum and then decreases to values observed in milk [1, 48]. Initially, casein in colostrum is reported to make 9.24%, while it is 2.5-2.8% in milk [49]. Caseins are essential in the digestion of important micronutrients. Formation of micellar structures around minerals or trace elements, are leading to a better uptake rate within the digestive tract [50-51]. Casein-derived bioactive peptides, which exert anti-oxidative, immunomodulatory activity and cytomodulatory effects, are generated through enzymatic hydrolysis, fermentation or gastrointestinal digestion [52].

Isaacs [53] described that milk lipids exhibit antimicrobial properties during digestion. Fatty acids as palmitic (C16) and myristic acid (C14) are the most abundant fatty acids occurring in higher quantities [1, 54]. They provide antimicrobial activity released by lipases in the gastrointestinal tract of humans [53]. Microbial bindings to the gastrointestinal tract can be prevented through attachment of lipids on the bacterial receptors [55]. The summary of these fundamental bioactive components and elements occurring in bovine colostrum is given in Figure 1. The cell types observed in bovine colostrum can synthesize macrophages, monocytes and T and B lymphocytes, which are immune cells [56]. All these bioactive factors and their effect on human health is well described in several research articles [6-7, 42, 56].

3. Microbiological Quality of Colostrum

Bacteria in raw colostrum and milk is of vast concern. Pathogenic bacteria present in milk and milk products have been reported to account for 1-5% of bacterial foodborne disease outbreaks in humans in the industrialized countries [18]. Bovine milk and colostrum serve as nutritious growth media for bacteria. The psychrotrophic bacteria spoilage the contaminated milk through both lipolytic and proteolytic activities [57]. The hygiene of the calving cows is crucial, as particularly feces contain several pathogenic bacteria [16]. Furthermore, the storage conditions on the dairy farm as well as before and after processing affect the bacterial loads within the colostrum. At refrigerated temperatures, most bacterial species grow slower and the storage can be prolonged [17].

The presence of high counts of bacteria is undesirable, because they undermine the quality of raw colostrum. Bacteria can grow, digest and harm colostrum by generating toxic agents or spoilage by-products, which possibly can prevent the beneficial effects of colostrum components [58]. Therefore, this study suggests heat processing of bovine colostrum. In the following, both pathogens and spoilage bacteria as well as typical bacterial infections are described.

3.1. Regulations on Bacterial Counts

For the overall assessment of colostrum quality, the standard plate count (SPC) of raw colostrum samples is of significance. The regulations are the same as for raw bovine milk given for the SPC, the total coliform count (TCC) and stating the absence of other infectious bacteria [19]. Regulation (EC) 853/2004 states that raw milk and colostrum must have a SPC at 30 °C of $\leq 10^5$ CFU/mL [18-19, 59]. Eight hundred and twenty-seven (827) samples were analyzed in a survey carried out in the USA by Morrill et al. [11], who found that 43% had a SPC $\geq 10^5$ CFU/mL and 16.9% had $> 10^6$ CFU/mL. Godden et al. [60] reported an average count of $4 * 10^5$ CFU/mL CFU/mL in 518 samples tested, meanwhile the study by Houser et al. [10] with 55 samples showed an average count of 10^6 CFU/mL. Half of the colostrum samples should on average be discarded based on the above the mentioned regulations, because such products represent a risk when consumed [11, 61]. Additionally, raw milk products in general possess a threat due to the contamination with zoonotic pathogens [18].

3.2. Bacteria Occuring in Colostrum

The major bacterial species being zoonotic pathogens, i.e. causing diseases in both animals and humans, and causatives of foodborne diseases include *S. aureus*, *Salmonella* spp., *Campylobacter* spp., *L. monocytogenes*, *E. coli* and *Bacillus* spp. [62-63]. Colostrum along with poor hygiene represents a potential transfer route for both bacterial infections and bacterial intoxications causing diseases [20].

Zoonotic bacteria derived from non-human origin can infect humans with a transferable disease [63]. The microbial contamination has to be monitored to prevent transfers to human population [10]. In general, disease caused by bacteria in food can be divided into infections and intoxications. Intoxications are evoked by secretion of toxins of specific pathogens, causing food poisoning [63]. These bacterial species include e.g. *Staphylococcus* spp. [64], *E. coli* [19] and *B. cereus* [65]. Infections on the contrary are induced by ingestion of food containing living pathogenic cells [63].

S. aureus of bovine origin, a major zoonotic pathogen, can lead to a wide range of infectious diseases for humans due to its risk to develop antimicrobial resistance [63, 66]. Houser et al. [10] found *S. aureus* to be present in 42% of 55 colostrum samples and Fecteau et al. [9] in 7.3% of their 234 samples. Lima et al. [14] performed the identification using 16S rRNA analysis. Furthermore, Fecteau et al. [9], Lindner et al. [67], and Derakhshani et al. [15] have reported *Staphylococcus* spp. in colostrum. Lindner et al., [67] also reported *S. chromogenes* and *S. pseudintermedius* in colostrum.

Salmonella strains are involved in foodborne outbreaks [63, 68] through diverse virulence factors, which cause infections in several host species [69]. Houser et al. [10] discovered presence of *Salmonella* spp. using PCR assessment in 15% of 55 raw bovine colostrum samples. The emerging risk of multidrug resistant *Salmonella* strains of bovine origin makes it a threat to human health [68].

L. monocytogenes is a Gram-positive bacterium, which causes the illness listeriosis and affects various human groups with reduced resistance seriously. The fatality rate is reported to be as high as 30%. Presence of *L. monocytogenes* in bovine colostrum has been described. A study in Japan revealed the contamination with *L. monocytogenes* in 7.6% of 210 samples [70].

E. coli strains in bovine colostrum are highly variable and can also be environmental bacteria. Only a few strains cause infections, while others are not pathogenic [66]. According to Fecteau et al. [9], the *E. coli* count exceeded 1,000 CFU/mL in 3.8% of the 234 samples.

Bacillus spp. are also considered to be an important zoonotic pathogen in milk [62]. In colostrum, Fecteau et al. [9] have detected *Bacillus* spp. presence in 15.4% of 234 to be above 1,000 CFU/mL. Lindner et al. [67] identified *B. circulans* in colostrum using 16S rRNA analysis.

3.3. Bovine Pathogens

Mastitis is characterized as being the inflammation of the mammary gland parenchyma and is considered a highly prevalent infectious disease in dairy cowherds, affecting 95% of American dairy herds [14]. Infection leads to reduced milk yield and changes in milk composition. Furthermore, it shortens the productive life of affected cows [71]. Economically, mastitis is considered a significant burden for the dairy farms [14].

Mastitis causing bacteria includes *Streptococcus uberis* [69], S. *agalactiae* [10], *S. dysgalactiae* [69], *Staphylococcus aureus* [72], *Corynebacterium* spp. [15], *Mycoplasma bovis* [73], *E. coli* [66] and *Trueperella* pyogenes [74]. All above have been reported to be present in bovine colostrum.

S. uberis is an environmental pathogen [66] and it is reported to be responsible for 20-30% of the clinical mastitis infections [69]. In a study by Fecteau et al. [9], *S. uberis* was detected in 20.5% of 234 colostrum samples. *S. uberis* is strictly an animal pathogen causing mastitis. It has not been found to be harmful to humans [66].

The total *Streptococcus* counts are also monitored, as streptococci can be both environmental and contagious. Houser et al. [10] reported the count of *Streptococcus* spp. to be above 500 CFU/mL in 71% of 55 samples. Studies by Fecteau et al. [9] and Gelsinger et al. [58] found *Streptococcus* colonies in colostrum. Humans should avoid intake of *S. bovis*, because it is associated with bacteremia, meningitis, endocarditis and colorectal cancer [62]. Its effect is reinforced by chronic interaction between *S. bovis* and human immune response especially in susceptible hosts [75]. Fecteau et al. [9] reported occurrence of more than 1,000 CFU/mL of *S. bovis* in 7.3% of 234 samples. Furthermore, *S. agalactiae* is known to cause several diseases in humans including gastrointestinal infections in infants, septicemia, urinary tract infections (UTIs) and mastitis in adults [66, 76]. Houser et al. [10] revealed occurrence of *S. agalactiae* in 2% of 55 colostrum samples. Opposite, *S. dysgalactiae* is regarded as a contagious environmental *Streptococcus* strain not yet reported to be harmful to humans. Fecteau et al. [9] has reported the presence in 1.3% of the 234 colostrum samples.

Lima et al. [14] reported presence of *Mycoplasma* spp. in bovine colostrum. *M. bovis* is a pathogen, which causes respiratory disease, mastitis and pneumonia in cows [73]. According to Gille et al. [77], it was detected in 1.9% of 368 colostrum samples.

Fecteau et al. [9], Lima et al. [14] and Derakhshani et al. [15] have described the general occurrence of *Corynebacterium* spp. in bovine colostrum. Fecteau et al. [9] stated that *Corynebacterium* spp. was present in 13.2% of the 234 analyzed colostrum samples. *Corynebacterium bovis* is regarded a causative agent of mastitis and is described to be a rare human pathogen [78]. As much as 67.5% of the *Corynebacterium* strains from milk of mastitis-infected cows were identified as *C. bovis* [79].

T. pyogenes causes both bovine mastitis and other bovine diseases [74]. Fecteau et al. [9] reported *T. pyogenes* counts of > 1,000 CFU/mL in 0.8% of 234 colostrum samples. In humans, *T. pyogenes* can cause endocarditis. Application of antibiotics in the dairy industry facilitates the emergence of multidrug-resistant strains for all hosts [80].

Mycobacterium avium ssp. *paratuberculosis* (MAP) is causing paratuberculosis in cows. Paratuberculosis is also referred to as Johne's disease and characterized being a chronic granulomatous infection of ruminant intestines [81], presenting an economic burden for the dairy industry [82]. Both colostrum and milk act as potential transfer routes in spreading the disease among cattle. The shedding of the bacteria by infected cows mainly happens through feces, but it can also be excreted in colostrum [83]. Besides the threat for bovine health, a likely connection between MAP and Crohn's disease in humans is suspected, but not proven, to be of zoonotic risk [81-82]. In humans, MAP can also cause tuberculosis infection [62, 83]. Streeter et al. [84] reported the presence of MAP in 6.4% of 126 colostrum samples, while Pithua et al. [85] discovered it in 33.7% of 205 samples.

Coliforms, a group of bacteria prevalently appearing in human and animal feces, are used as indicators for the occurrence of fecal contamination in milk products [86] and as signs of poor teat treatment or inadequate refrigeration [87]. Dos Santos et al. [88] and Derakhshani et al. [15] have confirmed the presence of Enterobacteriaceae in colostrum. Coliform bacteria, e.g. *E. coli*, can be a source of bovine mastitis infection [89]. Certain coliforms, e.g. enterohemorrhagic *E. coli*, can be pathogenic to humans and others are non-pathogenic [86]. Emerging antibiotic resistance in coliforms of veterinary origin is of special concern for humans [90].

Pseudomonas spp. are non-fermentative Gram-negative rods [9]. Their presence can lead to infection. *P. aeruginosa* has been described being a pathogen inducing pneumonia, UTI, meningitis and enterocolitis in humans [64]. *P. aeruginosa* has not yet been reported present in bovine colostrum, but *Pseudomonas* spp. have been found through 16S rRNA analysis [14-15].

Acinetobacter spp. have been described to be present in colostrum. Both Lima et al. [14] and Derakhshani et al. [15] showed positive results for *Acinetobacter* spp. using 16S rRNA analysis. Kröger et al. [91] also reported a draft genome sequence of *Acinetobacter junii* MHI21018, which was isolated from bovine colostrum. *A. junii* has been reported to cause septicemia [91]. Additional bacteria, reported to occur in raw colostrum, is summarized in Table 1.

Table 1. Harmful bacteria discovered in bovine colostrum

Contaminants	Source	Pathogenic potential in humans
Alcaligenaceae	[15]	Wound infection, pneumonia and sepsis [92]
Brachybacterium sp.	[67]	Thermoduric spoilage bacterium [93]
Cellulosimicrobium funkei	[67]	Opportunistic pathogen, endocarditis [94]
Cutibacterium acnes (formerly *Propionibacterium acnes*)	[67]	Endocarditis [76], commensal in human skin microbiome [95]
Enterococcus spp.	[9]	Enterococcal infections, urinary tract infection (UTI) and endocarditis [76]
Fusobacterium spp.	[14]	Endocarditis, UTI and sepsis [76]
Halomonas spp.	[14]	Bacteremia [96]
Macrococcus caseolyticus	[67]	Close relation to human pathogen staphylococci [97]
Micrococcus spp.	[9]	Endocarditis [76]
Paenibacillus barcinonensis	[67]	No data on effect on humans
Paenibacillus graminis	[67]	No data on effect on humans
Pasteurella spp.	[9]	Empyema, Tularemia and Brazilian purpuric fever [76]
Porphyromondaceae	[14]	Empyema and sepsis [76]
Proteus spp.	[9]	Endocarditis and UTI [76]
Stenotrophomonas spp.	[15]	Endocarditis and UTI [76]

3.4. Probiotic Bacteria

Probiotic bacteria are beneficial viable microorganisms employed both in food and drink as well as in medical health products [7, 98]. They mainly consist of lactic acid bacteria (LAB), *Bifidobacterium* spp. and *Enterococcus* spp. [64]. The human intestinal microflora mainly consists of *Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* spp., *Eubacterium* spp., *Peptococcus* spp. and *Peptostreptococcus* spp. among others in lower quantities [99].

Bifidobacterium spp. is commonly used as a probiotic strain due to acclaimed health benefits and overall presence in the gastrointestinal tract. There are rising interest especially towards *Bifidobacterium,* as it is a protective agent against infectious diseases. It helps to improve the immune response and to reduce symptoms of irritable bowel syndrome, ulcerative colitis, allergic diseases and atopic dermatitis associated to immunoglobulin E [100].

Lindner et al. [67] confirmed the presence of *Lactobacillus casei* and *Bifidobacterium pseudolongum* in bovine colostrum. Evaluations of effects of *L. casei* and *B. pseudolongum* consumption has not yet been reported, but the presence of *Bifidobacterium* spp. in the human intestinal microflora is presumably beneficial in digestion [98]. This can be explained amongst others by the production of conjugated linoleic acid (CLA) isomers e.g. by *Lactobacillus casei* and several *Bifidobacterium* spp. CLA isomers perform important physiological properties in humans, therefore the application of those in the dairy industry in probiotic foods or food supplements is of value [101]. More research on probiotic bacteria found in bovine colostrum is needed. These beneficial strains based on these results can be cultured and added in suitable levels to dairy products [99, 102]. Lima et al. [14] reported *Bacteroides* spp. in colostrum.

According to Lima et al. [14], an endogenous enteromammary pathway is the reason for intestinal bacteria to be able to migrate to the mammary gland. This is most probably facilitating the presence of gut bacteria e.g. genus *Prevotella* and family Ruminococcaceae in colostrum. Both Ruminococcaceae and *Prevotella* have been discovered in colostrum by 16S rRNA analysis [14-15]. *Prevotella* as well as Ruminococcaceae bacteria belong to the human gastrointestinal microbiota and they enable the digestion of e.g. plant polysaccharides [103].

LAB strains, which are recognized as generally regarded as safe (GRAS) organisms, inhibit coliforms and other bacterial pathogens [18, 104]. Santos et al. [88] detected LAB in colostrum samples through culturing. Furthermore, Vivarelli et al. [105] have showed that they have anti-carcinogenic effects.

3.5. Bacterial Effects in Colostrum

Certain bacteria can trigger diseases for both animals and humans, some also deteriorate the product quality. The bacterial count is increasing rapidly, when the colostrum is kept warm. A change in bacterial composition can be problematic and high bacterial counts can lead to a decrease in protein content [58, 104], Cummins et al. [106] reported a decrease in the acidity (pH) of the colostrum with high bacterial counts, especially when it was stored at warm temperatures, i.e. above 4 °C.

On the contrary, there are probiotic species, which secrete beneficial compounds as e.g. *L. casei* strains produce heteropolysaccharides, consisting of sugars and other constituents. Probiotics also synthesize exopolysaccharides or indirectly enzymes synthesizing polysaccharides, which have many health benefits for consumers. LAB also generates lactic acid through the digestion of carbohydrates. The biological activities include anticancer, antimicrobial, immunomodulatory and anti-inflammatory activity. Probiotics as ingredient can improve the quality of raw colostrum for human consumption [98-102].

4. Products of Bovine Colostrum

Nowadays, bovine colostrum as food is available on the market. Bovine colostrum for human consumption is collected and frozen on the individual farms and thereafter shipped frozen to processing facilities, where it is pasteurized and further treated through optional fat and lactose removal before spray- or freeze-drying to powder [7]. Available colostrum products include: 1) raw whole colostrum powder, 2) raw skim colostrum powder, and 3) industrially produced colostrum milk protein concentrate [35]. Currently, bovine colostrum is available in liquid form or as spray- or freeze-dried colostrum powder [8, 107]. It has also been used as nutraceutical. Whey formulations with high concentrations of bioactive proteins and peptides are accumulating immense interest among human health specialists [108]. The powder can also be marketed as dietary supplement in form of sachets, capsules or chewable tablets [7]. Fractionation of bioactive components out of bovine milk and colostrum yielding health-promoting foods is also gaining attention. This entails fractionation of caseins or whey proteins as well as isolation of LF, LPO or especially bovine colostrum's Igs [45]. There are also dairy products, in which bovine colostrum is used as an additive in cheeses, butter, yoghurts, kefir, fermented milk, milk powdered beverages, ice cream, jellies, nutritional bars, and ready-to-drink beverages [6-7].

5. Contamination Control On-Farm and in Processing

5.1. Contamination Risk On-Farm

The production including harvesting and storage of colostrum are the main factors in primary production determining the microbiological quality [61]. Pathogenic and spoilage microorganisms can enter the colostrum directly from the udder due to contamination, the environment, workers and contaminated equipment. Poor hygiene practices increase the risks [109-110]. Microbes may contaminate the colostrum during milking, processing, packaging, storage and transport [111].

Bacterial counts of colostrum derived aseptically from the udder contain relatively low counts of bacteria. Thirty-nine analyzed samples gave a mean SPC of 30 CFU/mL. The harvesting process is regarded a critical control point in colostrum production. Especially the pre-treatment of the gland and milking buckets are potential threats [17].

Transmission of bovine infections like mastitis, which is commonly caused by *S. uberis* or paratuberculosis infection by MAP, is described to occur due to shedding of bacteria from feces [69]. Feces of infected cows may contain MAP in concentrations of $>10^8$ CFU/g [81]. Stewart et al. [17] reported the TCC to be quite low directly on the udder, the average being 8 CFU/mL in 39 samples. The numbers vastly increase up to 50,000 CFU/mL during further storage without processing. The number of coliforms present is highly variable, ranging between a minimum of zero to a maximum of $4 * 10^6$ CFU/mL [10].

Besides the harvesting, storage conditions of colostrum are critical [106]. EU regulations state, that colostrum must immediately be cooled below 8 °C and stored separately. During transportation, the temperature must be kept below 10 °C [19]. Phipps et al. [61] stated that refrigerated storage of colostrum yields lower bacterial contamination counts than storage at ambient temperatures. Cummins et al. [106] analyzed the bacterial counts in colostrum stored at different temperatures, i.e. 4, 13 and 20 °C for 72 h. Six samples were analyzed and showed most significant increase while stored at 20 °C from initial 10^6 CFU/mL to $8 * 10^8$ CFU/mL, at 13 °C it reached 10^8 CFU/mL and at 4 °C it increased to $2 * 10^6$ CFU/mL. Therefore, colostrum should be stored at temperatures ≤ 4 °C, while the first 6 hours after milking are critical [106]. Subsequently, colostrum should be cooled as soon as possible after harvest to avoid the fast accumulation of high bacterial loads, which should be monitored accordingly. Morrill et al. [11] confirms that the counts in refrigerated samples are greater than in frozen samples.

5.2. Risks in Processing of Bovine Colostrum

The following steps affect the colostrum quality prior to and during processing: 1) cow's health status, 2) milking hygiene, 3) chilling practices and efficiency, 4) cleanliness of milking equipment including equipment design, maintenance, cleaning and disinfection, 5) personnel hygiene, 6-8) chill temperatures during packaging, storage and transportation as well as 9) heat treatment taking into account soiling of the heat exchanger plates during use [111-112]. Precautions done by the dairy farmers cannot completely guarantee that the colostrum is free from harmful bacteria.

The industrial processing of bovine colostrum becomes essential with consideration of potential pathogens being inherent in raw dairy products [18, 20]. The colostrum must be treated either decentral at the dairy farm or central at a dairy processing site (Figure 2). There are several techniques utilized to improve the colostrum quality, e.g. pasteurization either batch wise or continuously with high temperature, short time (HTST) or low temperature, short time (LTST) pasteurization [20], microfiltration and high-pressure processing [4] and fermentation [113]. More information on the techniques can be found in this chapter.

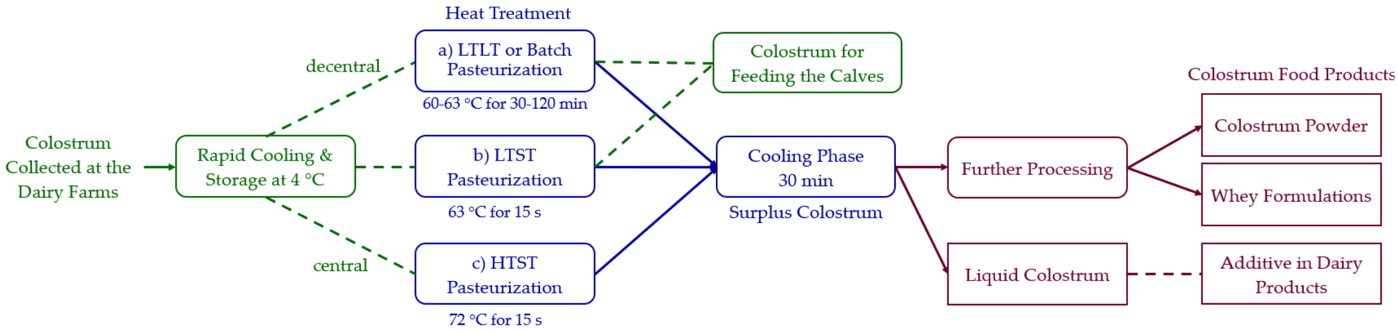

Figure 2. Feasible colostrum heat treatment procedures are either decentral on-farm or central at the dairy. The steps within the box display options for heat treatment of colostrum, which can be: 1) pasteurization in batches i.e. Low Temperature Long Time (LTLT) pasteurization, 2) continuous Low Temperature Short Time (LTST) pasteurization or 3) continuous High Temperature Short Time (HTST) pasteurization. A part of the heat-treated colostrum is used as feed for the calf. The rest is available for use in food.

5.3. Heat Treatment

Different industrial standards include batch pasteurization in which the colostrum is heated to 63 °C for 30 min is also called LTLT-pasteurization can be employed to minimize viable bacterial counts [114]. HTST pasteurization is commonly replacing the batch method. It gives similar effects but more efficiently e.g. at 72 °C for 15 s. Pasteurization is normally rapid heating of liquids to inactivate bacteria. LTLT heat treatment is the most convenient treatment for farms with small amounts of colostrum [18, 20, 114]. These treatment options are also described in Regulation (EC) No. 852/2004, Annex II, Chapter XI for treatment of raw colostrum or milk [109]. By the application of these heat treatment methods, the product will not be sterilized, because sterilization entails killing of all viable bacteria. With pasteurization, most of the harmful organisms in milk will be inactivated or reduced to a secure microbial level in the product [20]. An additional process described for milk heat treatment is LTST pasteurization, in which temperatures between 58-68 °C are used for 15-30 s. The lower the temperature is, the longer time is required. This processing technique focusses on the inactivation of psychrotrophic bacteria, which can release heat-resistant enzymes, e.g. protease and lipase into raw milk. Commonly, this process is followed by consequent further treatments [115].

A report by Johnson et al. [116] states that the feeding of heat-treated colostrum led to an increased IgG absorption rate, resulting in elevated serum IgG levels. Firstly, this can be explained by the lower microbe concentration of e.g. coliforms within the colostrum, which could bind free Igs [20, 60]. This is prevented by heat inactivation, leaving free Igs. Secondly, a protein denaturation caused by heat processing results in less interference for IgG receptor sites by other proteins [20]. Godden et al. [60] discovered a higher serum IgG concentration in calves fed heat-treated colostrum (18 mg/mL) compared to those being fed fresh colostrum (15 mg/mL) by the analysis of the upbringing of 1,071 newborn calves. Whether this phenomenon is also applicable in bovine colostrum digestion in humans remains to be analyzed.

Godden et al. [117] analyzed batch heat treatment of colostrum inoculated with *M. bovis* (10^8 CFU/mL), *L. monocytogenes* (10^6 CFU/mL), *E. coli* O157:H7 (10^6 CFU/mL), *Salmonella enteritidis* (10^6 CFU/mL) and MAP (10^3 CFU/mL). After keeping the colostrum at 60 °C for 30 minutes, no *M. bovis*, *L. monocytogenes*, *E. coli* O157:H7 and *S. enteritidis* was detected. Treatment at 60 °C for 60 min additionally inactivates viable MAP. The volume of the batch of colostrum treated was 30 L with a commercial on-farm pasteurizing system [117]. Earlier, MAP was used as an indicator for sufficient inactivation through heat as it is a relatively heat-resistant pathogen [18]. Inactivation of MAP through pasteurization might not be complete, which depends on the initial bacterial count [81].

Further Godden et al. [60] measured SPC and TCC of heat-treated and not heat-treated colostrum samples. An average SPC of 515,000 CFU/mL and TCC of

51,500 CFU/mL was detected for untreated, fresh colostrum, while heat-treated colostrum had an average SPC of 2,100 CFU/mL and a TCC of 90 CFU/mL. Heat treatment in this case comprised heating of colostrum in a commercial batch pasteurizer at 60 °C for 60 min [60].

Thermoduric bacteria, which to varying extent survive the pasteurization, e.g. *Enterococcus* spp. and *Bacillus* spp., are of risk to reduce the shelf life of colostrum and products thereof. Especially bacteria forming endospores, e.g. *Bacillus* spp., contaminate the colostrum after pasteurization [93]. In that case, pasteurization might not sufficiently eliminate the pathogens and other processing methods should be considered.

The HTST pasteurization can be as efficient, i.e. by keeping the liquid at a higher temperature for a shorter amount of time than in normal pasteurization. Stabel et al. [118] analyzed the inactivation of MAP inoculated colostrum by using a commercial on-farm HTST pasteurization unit. Survival of MAP and remaining IgG concentration were tested and examined at two temperatures. The viable count in colostrum decreased from 10^5 CFU/mL to 2 CFU/mL, when kept at 67 °C for 15 s with a post-pasteurization period of 30 min. At identical conditions, no viable MAP was detected directly after treatment when kept at 72 °C [118].

The bacterial inactivation can be improved and loss of bioactive agents can be diminished through process optimization, which has been summarized in Table 2. The IgG concentration is given in most articles and therefore used as immediate comparison value. Regarding most of the other immune components, there is less information available. HTST pasteurization e.g. will lead to the inactivation of 50% of the initial LPO activity [42].

Table 2. Summary of processing methods reported for colostrum treatment with resulting inactivation rate on the standard plate count (SPC) and total coliform counts (TCC) as log CFU/mL and detected loss in percentage (%) IgG concentration [4, 113, 117-119]

Method	Inactivation rate (log CFU/mL)	IgG concentration loss (%)
Low Temperature Long Time (LTLT) batch pasteurization, 30 min at 60 °C[117]	Inactivation of *Mycoplasma bovis*, *Listeria monocytogenes*, *Escherichia coli* O157:H7 and *Salmonella enteritidis*, but *Mycobacterium avium* ssp. *paratuberculosis* (MAP) was detected	No significant loss detected
LTLT batch pasteurization, 60 min at 60 °C[117]	Inactivation of *M. bovis*, *L. monocytogenes*, *E. coli* O157:H7, *S. enteritidis* and in three of four batches no MAP	No significant loss detected
LTLT batch pasteurization, 120 min at 60 °C[117]	Viable *M. bovis*, *L. monocytogenes*, *E. coli* O157:H7, *S. enteritidis* and MAP were not detected	No significant loss detected
High Temperature Short Time (HTST) pasteurization, 15 s at 67 °C[118]	MAP 4	22
HTST pasteurization, 15 s at 72 °C[118]	Inactivation of MAP in colostrum	27
Fermentation with *Lactobacillus plantarum* LUHS135[113, 119]	3[113]	No significant loss detected[119]
Fermentation with *Lactobacillus paracasei* LUHS244[113, 119]	3.3[113]	22[119]
Microfiltration (MF) and high-pressure treatment (HPP)[4]	> 6	27-64

5.4. Fermentation

A biological preservation method can be fermentation of colostrum with microorganisms that are GRAS for consumers and are commonly employed in starter cultures [113]. Bartkiene et al. [113] analyzed the effect of fermentation with *Lactobacillus plantarum* LUHS135 and *Lactobacillus paracasei* LUHS244 on microbial contamination of colostrum in combination with ultrasonication and dehydration. Both organisms are LAB. Fermentation enables biological and gentle preservation but on the other hand, it can provoke the formation of biogenic amines out of protein. In a current study, Bartkiene et al. [119] measured the effect of fermentation on the concentration of bioactive compounds, as IgA, IgM and IgG. Fermentation with *L. plantarum* LUHS135 showed no significant loss in IgG concentration. Moreover, during this study, antimicrobial activity against 15 pathogenic strains, including *P. aeruginosa* and *S. aureus*, was analyzed. The fermentation process in both studies entailed the inoculation of strain cultures and cultivation in a CO_2 incubator for 24 h at 30 °C [113, 119]. Fermentation with each of both *Lactobacillus* spp. led to the inhibition of 11 out of 15 studied microorganisms [119].

5.5. Microfiltration, High-pressure Processing and Subsequent Processing

It is possible to reduce bacterial counts in bovine colostrum with various physical methods. Gosch et al. [4] proposed and analyzed the combined treatment by microfiltration (MF) followed by high-pressure processing (HPP). Yet, the employment of crossflow MF includes the risk of forming a fouling layer on the filter membranes. This happens due to the micellar casein structures. Other ingredients besides bacteria are prevented to enter the permeate. In that, the protein concentration in colostrum is altered, resulting in a loss of serum protein. Therefore, a membrane pore size of 1 µm is suggested, which does solely not lead to a sufficient bacterial reduction. For that reason, HPP at temperatures below 40 °C follows the MF to reach colostrum of quality for human consumption. This HPP was performed at 400 MPa or 500 MPa over a time of 60 s. This treatment reduced the bacterial count by more than 6 log CFU/mL. Further, combined MF with HPP (at 400 MPa) leads to the loss of 27-64% of the initial IgG concentration. The comparison of bacterial reduction achieved by MF and HPP to conventional thermal heat processes with simultaneous results reveals less IgG inactivation with the new approach [4]. Another study by Borad et al. [107] describes the use of MF followed by ultrafiltration for the processing of skim colostrum and colostrum whey. Consequently, spray drying is performed with former addition of thermal protectants, as e.g. sugars. Overall, this method results in colostrum powders with 88.5% of the initial Ig concentration but this was only analyzed in pilot scale [107].

6. Process Design

6.1. Process Synthesis

Processing is described as a systematic series of actions designed to increase the value added to the food product [120]. In the process development system, the configuration of processing steps for desired and safely products are included. When determining the colostrum treatment process, attention is focused on ensuring food safety without destroying biological activity. Typical questions to be answered, when the process is developed, include: Which processing steps are required? What is the best type and size of process to use, and under which operation conditions? A minimum number of process steps is always the goal in an economically viable, efficient process e.g. there are a number of process options, which certify the safety of heat treatment and among these the most optimal option should be chosen. The first and simplest flow diagram is the block diagram (Figure 2), in which the various unit operations of the process are represented as simple blocks connected to each other by lines representing the process flow from one operation to another. In food processing, two top priority issues are ensuring food hygiene and preventing pollution. Wanniarachchi et al. [121] presents the food processing facility model, which classifies the food processing based on activities and risk levels in food processing into five areas, which are primary, secondary, utilities, warehouse, and administration [122].

6.2. Process Alternatives

The first step is a review of colostrum processing choosing between batch and continuous process. The batch process has been part of human activity throughout history. It remains used most of the time on a laboratory scale. The batch process is suitable for small-scale manufacturing in capacity. In small scale, investment in LTLT pasteurization is a possible method for heat treatment. According to the data in Table 2, no significant loss in IgG concentration has been observed for this method [60].

The bovine colostrum is brought from the farm to the dairy for processing. The collection options include refrigeration (4 °C), longer-term freezing or freeze-drying [3, 123]. Refrigeration at 4 °C in plastic containers maintains the Ig-properties up to 1 week [124].

For large-scale production, there are several possible thermal treatment processes available. Both LTST pasteurization and HTST pasteurization can be performed efficiently in a continuous plate heat exchanger. Lazaar et al. [125] principal numerical results point out that the turbulence depends on the angle of plate corrugations inclination. Therefore, in the case of colostrum processing, attention must be paid to the selection of the flow forms of plates of the plate heat exchanger and the distance between the plates, and possibly tested experimentally before. The colostrum feed enters the regeneration section, absorbs heat from the pasteurized colostrum stream, where after it enters the pasteurization section. Process integration can easily reach a 96% regeneration rate [126].

The use of membrane filtration methods i.e. microfiltration requires the separation of fat globules from bovine colostrum, thus this method brings one more process step. The combination of MF and HPP should be considered as an alternative to the treatment of colostrum and other heat-sensitive raw materials. [4]

Meraj et al. [127] have presented a novel pasteurization system for milk. It simulates the thermal modeling system of solar milk pasteurization operated through a number of fully covered semitransparent photovoltaic thermal integrated parabolic concentrators (N/PVT/IPC). Al-Hilphy et al. [128] presents a new non-thermal moderate electric field (MEF) process for milk pasteurization. There is no information on the effect of the two methods, N/PVT/IPC and MEF, on the loss in IgG concentration. In addition, knowledge of the technical maturity of the methods does not yet exist.

6.3. Economic Considerations

The cost estimates in food processing plants are generally based on experience information and are thus less accurate than in chemical process industries [129]. General estimation techniques are used for pre-investigative design. Parin and Zugarramurdi [130] presented an investment analysis for production cost estimates in food plants based on general mathematical clauses. This analysis could be used to compare investment costs in chemical and food processing plants.

From both financial and profitability point of view, the cost analysis of thermal treatment processes is manageable and scalable both upwards and downwards. A popular method for scaling is to use Guthrie charts of equipment cost versus capacity [131]:

$$C= C_0 \left(\frac{M}{M_0}\right)^n \quad (1)$$

where, C is equipment cost in capacity M_0, and C_0 is equipment cost in capacity M. The scale index, exponent n varies with a type of equipment, i.e. heat exchangers have the value 0.65 for n [129].

6.3.1. Equipment Costs and Efficiency, Non-dimensional

The key part of the manufacturing costs consist of both equipment and utilities in the process. In a book edited by Bartholomai [132] cost structures of various implemented solutions in food factories were showcased. In this review, costs of equipment in different thermal treatment alternatives were evaluated dimensionless. For operation costs, the energy cost is comparable between various pasteurization processes. The batch pasteurization process is estimated to one-tenth of cost for continuous pasteurization (Table 3). Similarly, the operation cost in terms of energy is five times the cost in batch pasteurization compared to continuous processing. Since, there is no significant difference between the methods in the reduction in IgG concentration, then optimization can be done directly based on the amount of processing of colostrum to be treated (Figure 2, Table 2).

The most reliable cost assessment method for food process equipment is to conduct budget intelligence from key equipment manufacturers or suppliers. However, pricing requires accurate and detailed information about the device sizing, material choices, operating and cleaning conditions etc. Another type of estimating the prices of food process equipment is to extract the unit processes into small parts and to compile transparent price information for the process device based on standardized parts e.g. price information on pumps is freely available on internet. The operation cost was estimated for the basis of the energy balance of the process and the price of electricity for household consumers in Germany (30.1 cents per kWh) and in Finland (17.3 cents per kWh) in 2019 [133]. Steam as the heating source can be used, if the pasteurization process is part of a large processing plant. In that case, steam can be produced in oil-powered steam generators, in which the energy price is 6 cents/kWh [134]. The equipment cost for the pasteurization process was estimated based on empirical information and the food process solutions presented in the book edited by Bartholomai [132]. Investment costs will increase tenfold, when the batch heat treatment becomes continuous. The continuous process allows for a high degree of regeneration of thermal energy, resulting in the cost of energy per unit falling to the tenth. If the energy source is steam, there is an energy cost of 4% more compared to the batch heat treatment process.

6.3.2. Bacterial Inactivation and Loss of Bioactive Agents

Data on the previously described processing techniques regarding bacterial and IgG inactivation rate have been summarized in Table 2. The IgG concentration is used as immediate comparison as most data is given. But the given IgG inactivation rates might not equal the amount of active antibodies, as the processing affects their functionality. Regarding most of the other immune components, there is less information available. HTST pasteurization e.g. will lead to the inactivation of 50% of the initial LPO activity [42].

6. Conclusions

Bovine colostrum, the milk secreted by cows after giving birth, invigorates newborn calves and supports their immune defense. It contains a variety of different antibodies for conferring passive immunity and for directly combating microbial infection caused by bacteria. Furthermore, about 70 indigenous enzymes have been identified in bovine milk as well as other bioactive components e.g. carbohydrates, (glycol-) proteins e.g. lactoferrin and caseins, growth factors, cytokines, lipids, enzymes, vitamins, and minerals.

The amount of bioactive components and elements are significantly higher in colostrum than in milk. Due to this, the variety of nutritive beneficial components with chemical/functional activities, bovine colostrum is also of interest for human consumption since healthy cows produce colostrum in excess of the calf's need. The use of bovine colostrum as food and food supplement for human consumers is increasing interest. There are benefits for all persons especially those being active in athletic performance and for those wanting to prevent or treat gastrointestinal, respiratory, inflammatory, and bone development diseases.

However, there are risks of the growth of both spoilage and pathogenic bacteria in the bovine colostrum, which can lead to the spread of zoonotic diseases from bovine origin. In addition, the product quality is lowered due to the contamination, which can be a result of poor harvesting and subsequent storage conditions. This review overviews the literature on microbial hazards in bovine colostrum, which shows the need for treatment before consumption. There are suitable processing techniques listed in the review. The design of a treatment process contains three options for heat treatment of bovine colostrum decentral or central. The procedures presented focus on ensuring the food safety and keeping the high nutritional values for consumers. The review pinpoints that processing of bovine colostrum at the dairy farms with colostrum production big enough can improve the quality and extend the shelf-life of it.

On-farm processing would improve the quality of bovine colostrum used both at home and in small processes, e.g. as ingredients. The traditional pasteurization methods are cost-effective compared with newer processing methods e.g. HPP. The investment costs of the pasteurization process is adjustable in accordance with the production capacity of bovine colostrum treated. The pasteurization process does not increase the costs by bringing in other consecutive cost-intensive process steps into the production. Beyond this, studies on more optimized industrial scale heat treatment in combination with maintenance of nutritional values are required.

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