Review

A Comprehensive Review of the Variability of Bovine Colostrum Components and Their Effect on Neonatal Calf Physiology

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A Comprehensive Review of the Variability of Bovine Colostrum Components and Their Effect on Neonatal Calf Physiology

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Simple Summary: Colostrum is the "starter-kit" for every calf, containing nutrients and bioactive components that provides energy and protection against pathogens, and contributes to the maturation of the gastrointestinal tract. Components such as fatty acids, whey proteins, oligosaccharides, immune cells, and microorganisms are present in colostrum and are essential for the health and well-being of the newborn calf, so its importance should not be underestimated. There is limited information on the variation and importance of colostrum components other than IgG for the neonatal calf. In this narrative review, we aimed to discuss how colostrum components vary, what their role is in the nutritional aspect of the newborn calf and how they individually affect passive immunisation, gut maturation, thermoregulation, and energy supply processes.

Abstract: Most research on colostrum quality and colostrum management focuses on maternal IgG transfer to the newborn calf. However, in addition to being a source of antibodies, colostrum has other components that influence passive immune transfer, nutrition, gut maturation, and thermoregulation. In this review, the constituents in the bovine colostrum, as well as their variation, are explored and it is discussed the biological role of colostrum on the newborn calf. Protein is the nutrient in higher concentration and fat is the nutrient with the most variation. There is a pronounced amplitude in the total solids content of colostrum, but the average concentration does not vary much between studies (24.7%). Bovine colostrum major components can vary with several factors, such as the region, season, breed, dry period length, and nutritional aspects of the dam. Bioactive components, cells, and microbiome variability are less understood, besides IgG. Regardless, they play crucial distinct roles in the physiological development of the newborn. However, a multi-interactive effect between these components, cells, and microorganisms is more likely to occur. Recently researched components in colostrum like miRNA, nucleo(t)sides, the milk fat globule membrane, oligosaccharides, minor proteins, and the microbiome are examples of promising interest areas of study.

Keywords: bioactive components; cell; gut maturation; nutrition; microbiome; passive immune transfer; thermoregulation

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1. Introduction

Colostrum is the first lacteal secretion of mammals after parturition. It is highly energy dense and contains many bioactive compounds essential for the newborn's survival and development [1,2]. Colostrum is the 'starter kit' for any mammal, providing molecules for all the biological processes the newborn needs to survive now that it is no longer protected by the womb and nourished by the placenta [3,4]. The importance of colostrum is also species dependent. The placenta of the female ruminant, due to its physiological characteristics, does not allow the passage of macromolecules to the foetus, which prevents it from acquiring immunoglobulins during gestation, unlike other species such as humans [5,6]. This peculiarity makes it essential for ruminants to consume colostrum immediately after birth, since colostrum has a high concentration in immunoglobulins. In addition to hypogammaglobulinemia, the newborn ruminant also has other physiological abnormalities. Fortunately, in addition to immunoglobulins, ruminant colostrum contains nutrients like carbohydrates, proteins, fat, and minerals that provide energy for basic cell functions and thermoregulation [3,7]; it contains: i) many immune factors, antimicrobial peptides and immune cells that actively protect against specific pathogens and help to regulate and "teach" the newborn's immature immune system [8–10]; ii) endocrine factors that are crucial for the maturation and development of the gastrointestinal tract (GIT) [11]; iii) signalling molecules that modulate and programme gene expression and other cell-related regulatory functions [12,13]; and iv) microorganisms that help to establish the newborn's microbiota [14]. All these components are required because the newborn calf undergoes major morphophysiological changes in the first days of life as it adapts to extrauterine life [15], and during this time, it cannot initiate a proper immune response against pathogens [16].

Besides its importance for farm animals, colostrum, and mainly bovine colostrum (BC), is gaining popularity as a food ingredient [17], as a nutraceutical for humans [18,19], and is also being explored for potential applications in anti-tumour therapeutics for specific cancers [20]. Due to its nutritional value and low availability, BC has a high market value compared to other by-products of the sector [21], and its demand is projected to increase [22]. This heightened market value accentuates the significance of conducting research to enhance both the availability and quality of bovine colostrum (BC), both on the farm and throughout the processing stages.

Immunoglobulins, particularly IgG, are the most well-studied bioactive compounds, as colostrum quality is usually defined by its concentration in IgG [23–26]. However, calves that were fed maternal colostrum instead of colostrum replacer (that has a defined concentration of IgG) showed improved immunocompetence and higher body gains [27], which demonstrates the importance of the whole colostrum's matrix for the calf wellbeing. The nutritional value and other bioactive components of BC have received less attention from the academic community. Nevertheless, it has been noticed that colostrum contains a wide variety of properties other than the transfer of IgG which may be just as important. Growth factors are a good example and perhaps the second most studied component of BC. Immune cells have been studied for a long time and their importance as protectors and immune regulators is a given fact, but it seems that freezing deactivates these cells, which is very problematic as freezing colostrum for later use is a common practice on dairy farms. There are other preservation methods (such as fermentation) or colostrum management practices (e.g. prioritizing fresh colostrum, with proper calving management) that could help to preserve maternal cell function in colostrum, but these have not received much attention at present. Some other specific examples of bioactive components that are now receiving attention are the milk fat globule membrane (MFGM), oligosaccharides, lactoferrin, miRNA and nucleic acids, and the BC microbiome. It is known that the most studied components (mainly IgG) vary with season, maternal nutrition, breed, and age, but it is not known the variability of other less studied components. These compounds have different roles in protecting and developing the newborn calf, with possible long-term effects. However, there are still questions to be answered and further research is needed. Colostrum is a unique feed containing hundreds to thousands of different bioactive components [2], which means that there is still so much to learn about colostrum, and with new properties being

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discovered all the time and with the increasing need for production efficiency, reduced use of antimicrobials, and increased demands for animal welfare, research into colostrum is a must.

In this review, we aimed to provide a comprehensive list of the most studied nutritive and bioactive components in BC, indicating their concentrations and source of variation while explaining the role they may play in the neonatal calf. We also aim to identify compounds that deserve further research due to their potential importance for the neonatal calf.

2. Colostrum Components

Colostrum contains water, proteins, fats, carbohydrates (macronutrients), minerals and vitamins (micronutrients), as well as bioactive components such as immunoglobulins, hormones, enzyme inhibitors, growth factors and nucleic acids, albeit in smaller quantities. Some of these components can be described as having both nutritional and bioactive roles, however, despite their nutritional value, the importance of specific molecules goes beyond straightforward caloric content, which is why they will be considered as bioactive molecules in this review.

All nutrient and non-nutrient factors, except water, make up the total solids of colostrum, which is officially measured by the air-oven loss-on-drying technique (Method 925.23 of the AOAC), but can also be measured by refractometry on farm (Brix % refractometer) to assess the overall quality of colostrum [28]. Dry matter, protein, fat, and lactose analysis usually have official methods, but most of recent studies spanning approximately 25 years, these components have been analysed using an automated mid-infrared method, employing the Milkoscan equipment. Several peripartum dam-related factors significantly influence the yield of nutrient and non-nutrient components in colostrum. However, more knowledge is still needed to understand how these factors affect the production and transfer of these components other than IgG [29]. Factors such as farm size, prepartum feed, breed, parity, season, calving month, udder health, time interval from calving to milking, colostrum weight, and method of analysis can be a source of IgG variation [30–33]. Some of these factors also affect the nutrient component of colostrum, but there are still very few studies regarding this subject [34]. Table 1 shows the variability of the main components in the BC. The coefficient of variation was calculated to highlight the variability of each component across the literature. The authors tried to provide a broad range of studies across different regions, but the majority are concentrated in the subcontinent of North America. Specific information on each component is given in the respective subchapters.

Table 1. Variability of the main components of bovine colostrum in relation to breed, region, and method of analysis.

Component	Mean	S.D.	Min	Max	CV	n	Breed	Region	Method of analysis	Reference
TS (%)	23.9	3.41			14.3	10	H	Kansas, US	AOAC	[35]
	24.2					36	H	Cairo, Egypt	AOAC, 1999	[36]
	27.2	5.8	12.9	47.2	21.3	365	H	Isfahan, Iran	Milkoscan	[33]
	27.6	5.84	18.3	43.3	21.2	55	H	Pennsylvania, US	AOAC, 1975	[37]
	25.8	4.68			18.1	1074	H	Northern Greece	Brix	[34]
	24.7	0.51			2.1	72	H	Central Denmark	Milkoscan	[38]
	26.3		13.5	37		288	HF	Ontario, Canada and Minnesota, US	Brix	[39]
	25.3	4.9	11.0	42.0	19.4	709	HF	Évora, Portugal	Brix	[40]
	24.8	0.26	18	31	1.0	73	F	Pisa, Italy	Brix	[41]
	22.6	4.7	1.7	33.1	20.8	496	H + J	US	Milkoscan	[42]
	22.5	6.74			30.0	16	J	Kansas, US	AOAC	[35]
	27.7	8.76			31.6	99	J	Northern India	Gravimetric	[43]
	23.6	5.56	12.8	36.6	23.6	86	J	US	Dried overnight	[24]
	23.4	0.74			3.2	32	J	Central Denmark	Milkoscan	[38]
	21.2	4.43	10.5	28.6	20.9	58	J	Iowa, Canada	Brix	[44]
	24.3		10.4	52.6		569		Alberta, Canada	Brix	[28]

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Protein (%)	14.0	2.59			18.5	8	H	Kansas, US	Subtration	[35]
	16.6					6	H	Tuscia, Italy (TN)	Milkoscan 104	[45]
	13.9					6	H	Tuscia, Italy (HT)	Milkoscan 104	[45]
	13.5					36	H	Cairo, Egypt	AOAC, 1999	[36]
	14.9	3.32	7.10	22.6	22.3	55	H	US-PA	Kjeldahl	[37]
	18.5	4.9	4.90	29.6	26.5	365	H	Isfahan, Iran	Milkoscan	[33]
	17.8	3.97			22.3	1074	H	Northern Greece	Milkoscan	[34]
	14.7	3.51	4.55	25.22	23.9	559	H	Northen Italy	Kjeldahl	[46]
	15.4	0.42			2.7	72	H	Central Denmark	Milkoscan	[38]
	14.0	3.67			26.2	1226	H + F*	Northen Ireland	Milkoscan	[47]
	12.6	2.9	3.34	17.12	23.0	76	HF	Swiszterland	Milkoscan	[48]
	18.2	3.94	11.28	24.6	21.6	21	HF	Germany	Milkoscan	[48]
	16.1	1.64			10.2	8	F	Reading, UK	DairyLab II (NIR)	[49]
	12.7	3.3	2.60	20.5	26.0	542	H + J	US	Milkoscan	[42]
	13.1	4.08			31.1	99	J	Northern India	Kjeldahl	[43]
	23.6	5.07	9.16	31.63	21.5	88	J	US	Kjeldahl	[24]
	14.2	5.26			37.0	11	J	Kansas, US	Subtration	[35]
	14.6	0.62			4.2	32	J	Central Denmark	Milkoscan	[38]
Fat (%)	6.7	2.65			39.6	29	H	Kansas, US	Babcock	[35]
	6.0					6	H	Tuscia, Italy (TN)	Milkoscan 104	[45]
	5.9					6	H	Tuscia, Italy (HT)	Milkoscan 104	[45]
	8.0					36	H	Cairo, Egypt	Gerber	[36]
	6.7	4.16	2.0	26.5	62.1	54	H	US-PA	Babcock	[37]
	4.6	3.4	0.3	20.9	73.9	365	H	Isfahan, Iran	Milkoscan	[33]
	6.4	3.3			51.6	1074	H	Northern Greece	Milkoscan	[34]
	5.2	0.34			6.5	72	H	Central Denmark	Milkoscan	[38]
	4.6	3.04	0.12	14.95	66.1	557	H	Northen Italy	VDLUFA, 2013	[46]
	6.4	3.32			51.9	1226	H + F*	Northen Ireland	Milkoscan	[47]
	4.4	1.75	2.16	8.78	39.8	21	HF	Germany	Milkoscan	[48]
	5.5	2.8	1.32	14.21	50.9	76	HF	Swiszterland	Milkoscan	[48]
	3.55	1.82			51.3	8	F	Reading, UK	DairyLab II (NIR)	[49]
	5.6	3.2	1.0	21.1	57.1	531	H + J	US	Milkoscan	[42]
	3.3		0.1	8.7			J	US	Infrared	[24]
	3.4	0.51			15.0	32	J	Central Denmark	Milkoscan	[38]
	4.2	1.81			43.1	32	J	Kansas, US	Babcock	[35]
	8.0	7.96			99.5	99	J	Northern India	Gerber	[43]
Lactose (%)	2.7	0.91			33.7	8	H	Kansas, US	AOAC 1945	[35]
	3.2					6	H	Tuscia, Italy (TN)	Milkoscan 104	[45]
	2.6					6	H	Tuscia, Italy (HT)	Milkoscan 104	[45]
	2.5	0.65	1.2	5.2	26.0	55	H	US-PA	Colorimetric	[37]
	2.0	0.9	0.3	5.2	45.0	365	H	Isfahan, Iran	Milkoscan	[33]
	3.68	0.04			1.1		H	Central Denmark	Milkoscan	[38]
	2.15	0.73			34.0	1074	H	Northern Greece	Milkoscan	[34]
	2.36	0,51	0.74	4.06	21.6	577	H	Northen Italy	HPLC	[46]
	2.7	0.55			20.4	1226	H + F*	Northen Ireland	Milkoscan	[47]
	3.2	0.53	1.94	4.6	16.6	76	HF	Swiszterland	Milkoscan	[48]
	2.9	0.59	1.82	3.81	20.3	21	HF	Germany	Milkoscan	[48]

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	2.7	0.46			17.0	8	F	Reading, UK	DairyLab II (NIR)	[49]
	2.9	0.5	1.2	4.6	17.2	538	H + J	US	Milkoscan	[42]
	3.73	0.06			1.6	32	J	Central Denmark	Milkoscan	[38]
	2.4	0.77			32.1	11	J	Kansas, US	AOAC 1945	[35]
	3.0	0.20			6.7	99	J	Northern India	Lane-Eynon	[43]
	1.11	0.16			14.4	10	H	Kansas, US	Evaporation	[35]
	0.05	0.01	0.02	0.07	20.0	55	H	US-PA	AOAC, 1975	[37]
Minerals (%)	1.9	0.17			8.9	8	F	Reading, UK	DairyLab II (NIR)	[49]
	1.02	0.40			39.2	99	J	Northern India	Incineration	[43]
	1.22	0.14			11.5	16	J	Kansas, US	Evaporation	[35]

Were considered values only from first milking after birth. When not provided SD (standard deviation) was calculated from SE (standard error) with following formula: SD = SE x Sqrt(n). CV – Coefficient of variation was calculated based on the mean and SD reported in each reference. Total solids, dry matter, and brix were considered as the same component. Values missing were not reported. TS, Total Solids; H, Holstein breed; F, Friesian breed; HF, Holstein-Friesian breed; J,Jersey breed. *Mostly Holstein and Friesian.

2.1. Macronutrients

2.1.1. Total Solids

During the first few weeks of a calf's life, colostrum and milk are the primary sources of water. Voluntary intake of free water is low during this period and gradually increases with age, weight and dry matter intake [50,51]. The quality of colostrum is determined by the proportion of its non-water constituents, commonly referred to as total solids (TS). Most review articles on colostrum composition report the same mean value of 23.9% for the total solids content of BC [4,52,53], all of which (indirectly) trace back to a paper published in 1950 with Holstein cows [35]. However, more recent research should be considered when considering an overall value for BC. More recent papers also report a percentage of total solids similar to Parrish et al. [35], for example, a study with Jersey cows in the United States (n=96; 23.6%) [24], another with dairy cows from Switzerland (n=24; 24 %) [54] and other with Egyptian Holstein cows (n=12; 24.2%; [36]). A more extensive study (n=496) showed a higher variation, including differences between different regions of the United States [42]. The mean values ranged from 20.6 to 24.1%, and the minimum reported was low as 1.7% and the maximum reached 33.1%. In one study in Pennsylvania (n=55), the reported mean total solids reported (27.6 ± 5.8 %) was higher than the aforementioned studies [37]. Two other studies reported similar values in Iran with 365 Holstein cows [33] and in India with Jersey cows [43]. Jersey cows are known for their ability to produce milk with a higher concentration of solids than Holstein cows [55]. However, Morrill et al. [42] found no differences in the total solids of colostrum between Holstein (n = 494) and Jersey cows (n = 87). In contrast, a study in Brazil with Jersey cows reported higher values of TS when compared to other studies (31.3%; [56]). Local dairy breeds may have lower TS than Jersey and Holstein cows [43,57], but there are very few studies evaluating the colostrum composition of local dairy breeds to support this statement. There is still uncertainty regarding whether the reduced solids content in indigenous breeds has a similar impact on their offspring as it does on calves of Holstein or Jersey breeds. Further exploration is necessary to consider other factors such as calf size, which directly affects their dietary needs, and any regional discrepancies across countries.

These studies indicate a degree of homogeneity in the mean TS concentration of colostrum within the herd, with some possible variation between regions and breeds, as seen in Table 1. From these studies, a mean concentration of total solids of 24.7% can be inferred. This is slightly higher than that previously reported (23.9%) and above the limit for good quality colostrum (22%), which should estimate an IgG concentration of 50 mg/ml. However, the minimum values are represented by colostrum of lower quality (<22%), so it is still important to regularly assess colostrum quality [4]. This variation can compromise the calves' nutritional requirements and passive immune transfer if colostrum quality is not assessed prior to feeding or if the calf suckles directly from the dam [58].

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2.1.2. Proteins

Protein is the most abundant nutrient in colostrum and can be four times higher than in milk [53]. In dairy cow colostrum it is found at a concentration of 15.5%, ranging from 2.6 to 31.6% (Table 1).

Breed can affect the protein percentage in colostrum [43], and dairy cows with lower milk yield tend to have higher milk solids, yet, Morrill et al. [42] found no differences in colostrum protein content between Holstein and Jersey cows. The protein percentage of BC was lower in first and second parity cows than in cows with three or more parities [47]. Zarei et al. [33] and Soufleri et al. [34] found significantly higher values only in cows with four or more parities. At the same time, Morril et al. [42] found no differences in the protein % between parities. A higher protein % in colostrum was recorded during Autumn and Winter in Northern Greece [34] and during Winter in Northern Ireland [47]. In contrast, a study conducted in Egypt found no differences in colostrum protein content between seasons [33]. Nevertheless, it was observed that protein percentage was lower under heat stress conditions compared to thermoneutral conditions [45]. To further understand these variations, controlled experiments with consistent climatic conditions could help elucidate whether the observed differences are attributed to environmental factors such as temperature and photoperiod, or if they are confounded effects. There appears to be no significant effect of dry period length on protein percentage in BC [34], but a higher protein percentage was observed in colostrum from cows with a very long dry period (≥ 16 weeks) [47]. Intriguingly, cows receiving bovine rhinotracheitis vaccination produced 11g/L more protein in colostrum than unvaccinated cows [47].

Colostrum has a higher concentration of caseins (insoluble fraction) and whey proteins (soluble fraction) than milk [52]. Casein is present in the form of colloidal casein micelles (CM); these CM are larger in colostrum than in milk and are positively correlated with TS [59]. CM size is important in the processing of milk, but it is not known what role it may play for the newborn calf. Compared to milk, BC has a higher percentage of κ-casein, a lower percentage of α_s-casein and a similar percentage of β-casein [60]. Casein is involved in the transport of minerals and trace elements [53,61] and can also reduce proteolytic degradation, acting as an enzyme-inhibiting protein, preserving intestinal integrity and function (protecting epidermal growth factor from digestion) and aiding the activity of other biologically active peptides [62,63].

The whey fraction, in addition to its nutritional value, is composed of a large number of different proteins that play an important role in several biological processes [64], of which the most studied in milk are: α-lactalbumin, β-lactoglobulin, bovine serum albumin (BSA), immunoglobulins (IgG, IgM, IgA, IgE, and IgD), bovine lactoferrin and lactoperoxidase [65]. According to the literature, their concentration in bovine colostrum varies widely (Table 2). Some proteins such as casein, α-lactalbumin and β-lactoglobulin are synthesised in the mammary gland, while others such as immunoglobulins, BSA and lactoferrin are actively transported from the blood into the lumen of the mammary gland [23]. The importance of these proteins, for the human species is well established (Madureira et al., 2007), but the importance for newborn ruminants is not as well known, except for immunoglobulins. Colostrum proteins are a source of amino acids that can be used by the newborn calf for protein synthesis. However, the newborn gastrointestinal tract (GIT) exhibits a low proteolytic activity, and colostrum, despite containing trypsin inhibitors [66], still allows for some exogenous protein hydrolysis alongside intracellular protein degradation, which contributes to the amino acid supply [67]. Whilst some proteins, such as α -lactalbumin, can be rapidly hydrolysed to amino acids in the abomasum, caseins form a clot which undergoes slower degradation, thus providing a more spaced source of amino acids [3,67]. The curd formation retains caseins and lipids in the abomasum and slowly releases the whey fraction into the gut where it can be effectively absorbed. This may explain why calves without curd formation had lower serum IgG and IgA levels [68].

Immunoglobulins and β-lactoglobulin are proteins highly resistant to degradation [67]. Compared to milk, colostrum has a higher β-lactoglobulin/α-lactalbumin ratio, suggesting that β-lactoglobulin may have a specific role for the newborn [69]. β-lactoglobulin is involved in the digestion of milk lipids by improving the activity of pregastric lipases [70], enhancing the digestion of colostrum fat, promptly providing energy to the newborn. β-lactoglobulin also functions as a

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transporter of small hydrophobic ligands, such as retinol, cholesterol and vitamin D, to specific intestinal receptors [65]. α-Lactalbumin is present in the bovine colostrum and milk at lower concentrations than in human colostrum and milk, being involved in the synthesis of lactose [71]. BSA helps maintain oncotic pressure and is involved in binding and transporting of molecules such as fatty acids, bilirubin, hormones, and minerals [72]. It is transferred from blood to colostrum and is usually considered an indicator of the permeability of the blood-milk barrier [25,73,74]. It has been reported that a higher proportion of BSA in colostrum can affect the transfer of immunoglobulins from the intestinal lumen of the calf to the circulatory system, due to the limited capacity of the macromolecular transport mechanism [75].

Table 2. Concentrations of the major proteins in bovine colostrum.

Protein	Concentration	Reference
Caseins (αs, β, κ) (mg/mL)	48–89	[52][76] [77] [61]
α-lactalbumin (mg/mL)	2.0–3.8	[77][73]
β-lactoglobulin (mg/mL)	14.3–28.5	[73][77]
Bovine serum albumin (mg/mL)	0.45–2.5	[73][25][78]
Immunoglobulins (IgG, IgA, IgM) (mg/mL)	47–106	[79] [37][25]
Lactoferrin (μg/mL)	34–1960	[80][81][76][82]
Transferrin (μg/mL)	187–1070	[83] [80] [81][82]
Lysozyme (μg/mL)	0.4–1262	[79] [84] [85]
Lactoperoxidase (μg/mL)	22.8–22.8	[79]

2.1.3. Lipids

Lipids are the second most important component of colostrum after protein and are the main source of energy that the calf receives at birth. It is also the component with the highest variability, ranging from almost 0 to around 26%. The average percentage of fat is around 5.5% for dairy cows (Table 1). Breed can affect the fat percentage in colostrum [43] and dairy cows with lower milk production capacity tend to have higher milk solids, but Morrill et al. [42] found no differences in colostrum fat content between Holstein and Jersey cows. The fat percentage of BC is higher in primiparous cows than in multiparous cows [33,34,42,47]. Season may have a significant effect on fat percentage but this is likely to be region dependent., In Northern Ireland [47] and Northern Greece [34], colostrum fat percentage was higher in Spring. In Egypt, there were no differences between seasons [33]. Nevertheless, it was observed that fat percentage was lower under heat stress conditions compared to thermoneutral conditions [45]. There is not much information on the effect of dry period length on fat percentage in BC, but it seems that a dry period length of more than 60 days may result in colostrum with higher fat content [34,47]. In addition, a significant ($P = 0.001$) positive association was observed with fat percentage in BC and feeding straw and grass silage 7 to 9 weeks before calving and with vaccination against leptospirosis [47].

The main classes in the lipid fraction are triglycerides or triacylglycerols (TAG; the main class within the lipid fraction), phospholipids (the two main classes are glycerophospholipids and sphingolipids), free fatty acids (FA; short and long chain, saturated and unsaturated), eicosanoids and sterols (the most abundant of which is cholesterol) [7,86]. Lipids are an energy source, as they serve as structural components of membranes, are precursors for other molecules and act as actuators in various biological processes [87]. The lipids present in colostrum and milk are almost entirely in the form of milk fat globules (MFG), a lipid droplet containing mostly TAG, that is formed in the endoplasmic reticulum of the alveolar epithelial cells of the mammary gland [88]. MFG are then secreted by fusion with the plasma membrane of the alveolar epithelial cell, acquiring a peripheral bilayer called the milk fat globule membrane (MFGM), which contains polar lipids, cholesterol, glycoproteins, gangliosides, and enzymes in its structure [89,90]. The functions and mechanisms of action of MFG and MFGM are not fully understood, but they might contribute to antimicrobial effects, gut maturation, structural development, and establishment of early neonatal gut microbiota [89,91].

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Lipids also act as a source of energy, with FA oxidation providing energy to sustain gluconeogenesis [3]. This source of energy is particularly important in neonates, as lactose intake from colostrum is insufficient to meet glucose requirements [92]. In fact, a high postanal capacity to oxidise FA has been reported in several species [93]. Most of the energy comes from TAG, since they are the major constituents in milk fat, as around 95-98% of the bovine milk fat are TAG [94]. Gastric and pancreatic lipases hydrolyse TAG to FA and monoglycerides, which are absorbed in the intestine. These lipids then undergo several processes of re-esterification and hydrolysis until they reach the endothelial cells, where they can serve as a substrate for bioactive molecules, be oxidised to provide immediate energy, or be resynthesized into TAG, where they are transported to extrahepatic tissues such as muscle and adipose tissue for storage and later use as a source of FA and energy [87,93,95].

The energy provided with FA oxidation can also be used as a heat source, as newborns are born poorly insulated and have low metabolic rate [3,4,29]. The newborn calf is born hypoglycaemic and has very limited energy reserves, as only 3% or less of its body weight is lipids, most of which are structural [42]. It is speculated that the endogenous lipid content of a 40 kg newborn calf could support summit metabolism for 15h and that glycogen reserves would be depleted in ≤3h [96]. The situation may be exacerbated in cold environments, where hypothermia may occur, or if dystocia occurs [97]. Approximately 1.5% of calf BW is brown adipose tissue (BAT), mainly located in the perineal, prescapular, pericardial, and abdominal regions [98]. BAT contributes to non-shivering thermogenesis and is mediated by the cold-induced secretion of norepinephrine by the sympathetic nervous system, which stimulates the expression of the UCP1 protein. UCP1 uncouples electron transfer from ATP synthesis in the mitochondria of brown adipocytes, so the energy derived from FA oxidation is dissipated as heat instead [99]. This strategy allows hypothermia to be avoided until nursing occurs. However, some gestational factors can affect the amount of BAT that the newborn has [99]. In addition, BAT is gradually replaced by white adipose tissue during the first few days of life [98]. The high caloric content of colostrum (24.9 MJ/kg DM; [100]) makes it a good source of energy for heat production [101]. Therefore, the energy provided by colostrum is essential soon after birth to maintain normal functions and normothermia.

2.1.4. Carbohydrates

Colostrum contains carbohydrates in the form of lactose, oligosaccharides, glycoproteins, glycolipids, and nucleotide sugars. Lactose is the major carbohydrate in colostrum, with an average concentration of 2.8%, ranging from less than 1% to 5.2% (Table 1). Nazir et al. [43] observed that local dairy cows had lower lactose in colostrum than Jersey cows and Zarcula et al. [102] observed lower lactose levels in Romanian Black and White cows compared to Holstein-Friesian cows. Morrill et al. [42] found no differences in colostrum lactose content between Holstein and Jersey cows. The effect of parity on lactose content in colostrum is not marked when compared to protein or fat. However, there is a tendency to decrease when the number of parities increases [33,34,47], though this number varies between studies. In a study in Northern Ireland [47] and in Egypt [33], lactose percentage was higher in Autumn, but in a study in Northern Greece [34], lactose percentage was lower in Autumn compared to other seasons. Nevertheless, lactose percentage was observed to be lower under heat stress conditions compared to thermoneutral conditions [45]. As colostrum yield increased, lactose percentage also increased, but protein percentage decreased [34]. Lower lactose percentage was also observed in colostrum from cows with a very long dry period (≥16 weeks), but not in cows with a shorter dry period [47].

The concentration of lactose is lower in colostrum than in milk [7,35], since it has osmoregulatory functions, a high concentration of lactose would increase the movement of water from the cytoplasm of the mammary epithelium into the secretory vesicles and subsequently into the colostrum [7], which would reduce its overall quality, since it would have fewer components per litter. Thus, lactose concentration in colostrum increases with the time until colostrum collection, but other components concentration decreases [34,47]. The low levels of lactose in the BC, makes lipids the main source of energy available to the newborn calf in its first feed. However, lactose in colostrum is necessary to

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increase the water content of colostrum during the final phase of prepartum, otherwise the colostrum would be too dense for the calf to suckle [2].

Lactose is a disaccharide that, when hydrolysed, provides glucose and galactose as energy sources [103]. Calves are born hypoglycaemic and lactose intake from colostrum does not fulfil the calf's glucose requirements [92]. Therefore, calves must rapidly establish endogenous glucose production (glycogenolysis and gluconeogenesis processes) [3,92]. During the first hours of life, the calf can use the hepatic glycogen stored during the last phase of gestation to maintain a normal blood glucose concentration [92]. It has also been shown that colostrum feeding improves glucose absorption [104]. However, prolonged absence of feeding can lead to hypoglycaemia when there is no exogenous glucose intake, the glycogen stores are depleted and gluconeogenesis still needs maturation [92,104,105].

2.2. Micronutrients

2.2.1. Minerals

There is a large variation in the total mineral concentration of BC, which can vary with the time interval between parturition and milking [37,106,107], with the milking strategy [108] and with the number of milkings [107,109]. Unlike most colostrum constituents, mineral content does not seem to be negatively associated with colostrum yield [109], however, further research is needed in this area, as well with other variation factors. The most abundant minerals in colostrum are Ca, P, K, Na and Mg, while Zn, Fe, Cu and Mn are present in lesser amounts. Colostrum has a high concentration of Ca, P, Na, Mg, Fe, Se, Cu and Zn compared to milk, but a lower concentration of K and Mn [53,106,109,110]. Some minerals, such as Ca, P and Mg, seem to be in higher concentration in colostrum from first or second parity cows than in cows with three or more parities [107,109].

Each mineral has different physiological functions in the organism and therefore adequate levels of macro- and microminerals are essential for neonatal health and growth. However, the role of colostrum minerals in newborn calves is not fully understood and there is some disagreement as to whether maternal mineral supplementation improves colostrum quality [111]. In a recent study, both cow and calf showed increased levels of blood IgA, IgM and total antioxidant capacity following prepartum supplementation with Mn, Zn and Cu, but results were dependent on the source of supplementation [112]; protein, fat and lactose in colostrum did not change with treatment and immunoglobulins were not measured in colostrum. Ca is essential for skeletal development and absorption rates can reach 99% in young calves (10 days), decreasing with age to 22% in adult cattle [113]. Mineral supplementation over dietary requirements did not improve colostrum mineral concentrations in Brahman cattle [106], or sows [114], except for selenium. The efficiency of absorption is likely to decrease when dietary minerals, such as Ca, are supplemented above requirements [106,109], which also depends on the source of the mineral, as in the case of selenium [115]. More recently it has been shown that prenatal mineral and vitamin supplementation can alter the newborn calf microbiome at different sites of the body, affecting early microbial colonisation [116]. Research into the mineral composition of colostrum is limited, and therefore, very few conclusions can be drawn.

2.2.2. Vitamins

Vitamins can also be included as bioactive components, but for the purposes of this review, they will be referred to as micronutrients. Colostrum is an important source of vitamins essential for the health and growth of the newborn calf, and delayed colostrum intake can impair cell growth and differentiation and increase susceptibility to infectious diseases [4,54]. Fat-soluble vitamins (vitamins A, E, and D) are present in higher concentrations in colostrum than in milk, but water-soluble vitamins (vitamins C and B complex) do not follow the same trend [7,37,52,117–122]. Compared to milk, colostrum has only slightly higher concentrations of vitamin C and within the B-complex B1, B2, B6, B9, and B12 can be higher in colostrum, B5 and B7 are lower and B3 seems to be equal to milk [7,53]. Nevertheless, vitamin C is the most concentrated vitamin in BC. Table 3 shows the

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concentrations of vitamins in BC, as well as their physiological role in cattle. There is a lack of recent research on the vitamin content of BC. As genetics and feeding strategies have changed in recent decades, it may be relevant to update these values. Variation in vitamin concentrations in colostrum appears to be related to analytical difficulties rather than variable secretion patterns [53]. The factors influencing vitamin variation in bovine colostrum are not well understood but are known to be influenced by the time between parturition and milking and by the prepartum diet [7,123]. Heat treatment of colostrum (60 °C for 60 min) does not appear to affect levels of vitamin A, vitamin E or β-carotene [124]. More research is needed to understand what factors influence the vitamin content of colostrum, as vitamin deficiency can affect calf health and colostrum is a rich source of these molecules.

Table 3. Mean concentrations and physiological roles of vitamins present in the bovine colostrum.

Vitamin	Mean	Physiological role
Fat-soluble vitamins		
Vitamin A (μg/100 mL)	233–369	Immune function, cell-growth, and vision
Vitamin E (μg/100 g)	191–530	Antioxidant function.
Vitamin D (IU/100 g fat)	120–181	Ca and P absorption, bone health, and immune function.
Vitamin K (μg/100 mL)	> 2	Blood clotting and bone health.
Water-soluble vitamins		
Thiamine (B1) (μg/100 mL)	58–90	Energy metabolism and nervous system.
Riboflavin (B2) (μg/100 mL)	455–610	Energy production and cell growth.
Niacin (B3) (μg/100 mL)	34–96	Redox reactions (synthesis of NAD), energy metabolism.
Pantothenic acid (B5) (μg/100 mL)	224	Acetyl-transfer reactions (synthesis of coenzyme A), energy metabolism.
Pyridoxal (B6) (μg/100 mL)	15.0	Brain development, immune function, and production of haemoglobin
Pyridoxamine (B6) (μg/100 mL)	21.0	
Pyridoxine (B6) (μg/100 mL)	4.0	
Biotin (B7) (μg/100 mL)	1.0–2.7	Carboxylation reactions, glucose, amino acids, and fatty acids metabolism.
Folate (B9) (μg/100 mL)	0.75-0.8	Single-carbon-transfer reactions (nucleic acids synthesis), DNA and methionine metabolism.
Cobalamin (B12) (μg/100 mL)	0.2-60	Red blood cell production, neurological function, and DNA synthesis
Ascorbic acid (C) (μg/100 mL)	1620–3200	Antioxidant, immune function, skin, and blood vessels integrity.

Values were obtained from refs [7,37,52,117–122].

Vitamin A is important for protection against infection, immune function, cell growth and differentiation, maintenance of epithelial surfaces, and vision [125]. However, calves are born deficient in vitamin A and β-carotene; supplementing cows with vitamin A during the dry period can increase plasma retinol concentrations in calves [126]. Vitamin E appears to be transferred into colostrum by a mechanism involving low density proteins [7,127], it acts in the lipid phase as a radical scavenger, protecting phospholipid membranes from peroxidative damage and increasing the functional activity of neutrophils [128]. Vitamin B2 is found in higher concentrations in colostrum than other B vitamins. The concentration of B2 in colostrum exceeds the requirement of 100 μg/100 g of dry matter consumed by pre-weaned calves [129], suggesting a specific role for the newborn calf. To the author's knowledge, its specific role in the newborn calf has not been studied, but a deficiency of B2 results in mucosal lesions and growth related problems in young calves [130]. Calves can be born with vitamin D deficiency and can remain at low levels throughout the pre-weaning period, which has been shown to affect the immune system [122,131]. Cows are able to synthesise vitamin C primarily in the liver [132]. However, calves do not begin to synthesise endogenous vitamin C until about 2-3 weeks of age, making them dependent on the vitamin C provided by milk [133]. Cases of scurvy (a sign of vitamin C deficiency) have been reported in calves [134]. Non-colostrum-fed calves with a plasma vitamin C concentration of less than 0.15 mg/dl showed active infections and swollen navels, whereas injections of 500 mg/d alleviated the symptoms [133].

2.3. Bioactive Components

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Bioactive components (also known as nutraceuticals) are natural essential and non-essential molecules that act in the animal organism, usually with health benefits beyond basic nutritional value [135]. Compounds such as vitamins, hormones, growth factors, certain proteins, carbohydrates and lipids, as well as molecules such as nucleotides, polyamines and miRNA have been identified as bioactive components in colostrum [11,13,29,36,76,136–139]. These substances can be either of blood origin or produced in the lactocytes of the mammary gland [136].

Bioactive components from colostrum stimulates the development and function of the GIT, modulates the GIT microbiota, and provides local protection. There are multiple receptors for bioactive components in the GIT that trigger multiple events, making it difficult to explain a specific factor function [140]. Although there are many bioactive components in colostrum [2], only a few have been the target of research. Therefore, only the currently most relevant bioactive components will be reviewed in terms of concentrations and functions.

2.3.1. Bioactive Proteins

In addition to being a source of amino acids, the proteins in colostrum can perform several functions for the newborn. These proteins are found in the whey fraction and some of them have already been mentioned above. These bioactive proteins act through a variety of mechanisms, but their role is largely related to host defence.

Immunoglobulins

Colostral immunoglobulins are responsible for protecting the immunologically naive newborn calf against pathogens by activating and regulating the innate immune system. Although there is still much to learn, they have been extensively studied and reviewed in other papers, so only a brief mention of their transport mechanisms and concentrations in colostrum follows.

Immunoglobulins are a family of high molecular weight proteins with similar physicochemical properties and antigenic determinants [141]. The main immunoglobulin classes present in the bovine colostrum are IgG, IgA, and IgM [23], with IgD and IgE also present [4]. IgG is the predominant immunoglobulin in bovine colostrum, whereas IgA is predominant in primate colostrum [142]. IgG represents over 50% of the total protein of dairy cow's colostrum [143]. IgG is divided into three subtypes: IgG1, IgG2, and IgG3 [143]. IgG1 predominates over IgG2 in bovine colostrum by approximately 7:1, although blood concentrations are similar [144]. Nevertheless, IgG1 in blood decreases during colostrogenesis, which may be due to the passage of IgG1 from blood into colostrum [2]. IgG3 is present at even lower levels and has only recently been found in BC [143].

IgG in colostrum is found in concentrations ranging from 0.68 to 216.70 mg/mL, IgA concentrations range from 0.13 to 22.14 mg/mL and IgM from 0.18 to 14.01 mg/mL [25]. As IgG is the predominant immunoglobulin in colostrum, only this class is considered in quality assessment and a colostrum with 50 mg/mL of IgG is considered good quality colostrum [4]. However, for effective immunisation, factors such as the amount of colostrum ingested, the time between birth and ingestion, microbiological contamination and the method of administration must be taken into account [4].

IgG1 is selectively transported from the bloodstream into colostrum by specific receptors on mammary alveolar epithelial cells, a pH-dependent process called transcytosis [4,142], while IgG2 (and BSA) are recycled [145]. IgG1 and IgG2 differ in their amino acid structure, which may explain the different transport mechanisms [145]. IgA and IgM are produced in smaller quantities by plasma cells in the mammary gland [23]. While immunoglobulin transport appears to be selective at the mammary gland, the intestinal tract of the calf is non-specific for any immunoglobulin class until 24 hours after birth [23]. Immunoglobulins and complement proteins are resistant to gastric acids [3,53], which can increase their bioactive functionality along the GIT or allow absorption without compromising their structural integrity [89]. IgG1 can also be re-secreted into the GIT via FcRn receptors, providing local specific immunity [146,147].

Lactoferrin and Transferrin

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Lactoferrin (LF), a member of the transferrin protein family, is an iron-binding glycoprotein synthesised in the mammary gland and in other exocrine glands, and is therefore present in colostrum, milk, saliva, and in bronchial, cervicovaginal and gastrointestinal fluids [53,63,148,149]. LF is not present in the lacteal secretions of all mammalian species; for example, it has not been detected in dogs, rats and rabbits, but it is one of the most abundant glycoproteins in ruminant and human milk, although human milk is much more concentrated in lactoferrin than bovine milk (100 times or more) [149,150]. In contrast, rat and rabbit's milk is more concentrated in transferrin than human's milk, in which it is undetectable [151]. In cattle, both LF and transferrin are found in higher concentrations in colostrum than in milk [80], and transferrin is higher in blood [83]. The mammary gland secretes a high mass of LF during the dry period and colostrogenesis, and it may influence the release of IgG1 in colostrum by increasing intracellular pH, facilitating the release of IgG1 from FcRn, since this receptor depends on a pH < 6.5 or > 6.5 to either bind or release IgG1 [2]. The concentrations of LF and transferrin in bovine colostrum are shown in Table 2.

LF has been described as having many functions and may be relevant to GIT growth regulation in neonates [63]. Some functions are: ability to regulate iron absorption [152,153]; improvement of the intestinal epithelial barrier by promoting cell growth, decreasing paracellular permeability, and increasing alkaline phosphatase activity and transepithelial electrical resistance [154]; it can also be released from plasma neutrophils during infection or inflammation, possibly contributing to the activation of other immune cells, thus providing protection against pathogens [155,156] but it can also regulate the inflammatory process by inhibiting the progressive inflammatory cascade [53].

It appears that LF plays a greater role as a protective mechanism against infection in the dry mammary gland than in the lactating mammary gland, probably because of the low concentration of LF and the high concentration of citrate in the latter stage [156,157]. However, when LF is saturated with iron it loses its bacteriostatic effect [158], and given that citrate is an iron chelator, it seems that the low concentration of LF in the lactating mammary gland may be the main reason for the reduced antimicrobial effect of LF at this stage. Nevertheless, LF has a 300-fold higher affinity for iron than transferrin, which may not be relevant at physiological pH but allows LF to retain its iron-binding capacity in a more acidic environment, particularly in the presence of citrate [153]. LF has received increasing attention as a multifunctional protein, but its mechanisms are not yet fully understood.

Proline-Rich Polypeptide

Proline-rich polypeptide (PRP), also known as colostrinin, is a complex of at least 32 peptides present in colostrum of various species, including bovine [159,160]. PRP is probably derived from the partial proteolysis of annexin and β-casein [160,161]. The therapeutic effects of PRP have been studied in laboratory animals and in humans, particularly in patients suffering from Alzheimer's disease [161,162]. PRP can help prevent oxidative damage [163], which is important for newborn calves as they are susceptible to oxidative stress in the early stages of life [164]. It has also been shown to be effective in improving long-term memory in newborn chickens [165], and in modulating adaptive and innate immunity [166,167]. Immunocompromised rats infected with enterotoxigenic *E. coli* had reduced endotoxin levels and infected lymph nodes when treated with PRP [168]. PRP helps regulate cytokine production and has been shown to reduce allergic inflammation in murine [169]. These antiallergic properties could be helpful with calves-fed milk replacers since allergic reactions in calves to soybean flour in milk replacers have been reported [170].

Enzymes

Colostrum, like milk, contains many enzymes that perform functions associated with the host defence mechanism against microorganisms and oxidative damage, as well as many essential metabolic processes such as catalysis, lipolysis, and proteolysis.

Lactoperoxidase (LPO) is one of the most frequently mentioned enzymes in the literature. It is a glycoprotein, a member of the family of haem peroxidase enzymes, secreted by the mammary gland into colostrum [63,160]. The main biological function of LPO is to defend against microorganisms by generating reactive oxygen species (ROS), which is effective against a wide range of bacteria, but also

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has antiviral and tumoricidal activities [156]. This enzyme has been shown to be very resistant to proteolysis, highlighting its importance in the defence of the calf's GIT [156]. LPO and LF in milk lose activity during heat treatment above 70ºC for 30 minutes [171]. In this study, where different temperatures were tested, raw milk samples showed a lower growth rate per hour than treated milk of *Streptococcus thermophilus*, *Lactococcus lactis*, *Pseudomonas fluorescens* and *Escherichia coli* in whey, because as the temperature increased, the total protein content in whey decreased significantly, which also reduced the bacteriostatic activity in milk.

Lysozyme is an enzyme present in colostrum and milk [79,84,85] with specific hydrolytic activity against the peptidoglycan in cell walls of Gram-positive and -negative bacteria [172]. It is more effective against Gram-positive bacteria because their cell wall contains up to 90% of peptidoglycan [173]. Compared to humans or other species, such as horses, this enzyme is present in lower concentrations in bovine milk, probably too low to contribute effectively to the overall bacteriostatic and bactericidal activity [156,173]. The reported concentrations of lysozyme in bovine colostrum vary widely and are usually lower than other enzymes with antimicrobial activity (Table 2), but it generally increases after the first milking [174].

Other enzymes present in bovine colostrum include catalase, superoxide dismutase and glutathione peroxidase, which have antioxidant properties, and β-1,4-galactosyltransferase, lactate dehydrogenase, alkaline phosphatase and gamma-glutamyltransferase, which catalyse important biological reactions, and esterases, lipases (such as lipoprotein lipase), proteases (such as tissue plasminogen activator) and ribonucleases (such as ribonuclease II-1), as well as enzyme inhibitors, which are present in very high concentrations but rapidly decrease with time after birth [7,11,128,140,173,175–177].

Cytokines

Cytokines in colostrum are divided into interleukins, interferons and tumour necrosis factors, which are responsible for modulating the immune system [7]. Some of these pro-inflammatory cytokines, such as IL-1β, IL-6 and tumour necrosis factor-α (TNF-α), and acute phase proteins, such as serum amyloid A and haptoglobin, can influence the concentration of these molecules in the serum of calves during the first weeks of life [178]. Weaned pigs supplemented with colostrum also showed changes in cytokine mRNA expression in spleen and gut-associated lymphoid tissues, with increased expression of IL-2, IL-4, IL-10, IL-12 and decreased expression of IFN-γ [179]. IL-1Ra, IL-1β, IL-6, TNF-α and IFN-γ are present in higher concentrations in bovine colostrum than in mature milk; for example, IL-1Ra can be 180 times higher in colostrum than in mature milk [180], suggesting their importance as immunomodulatory factors in the newborn calf. Concentrations of these cytokines in colostrum can range from 77 to 5206 ng/mL [180]. There is still a lack of knowledge about the variation of other cytokines between the first milking and the subsequent milkings.

Cytokines are essential in the immune response, but some cytokines need tight regulation, otherwise the inflammatory process can have nefarious effects on the organism, such as IL-6, which plays important functions in inflammatory processes at the intestinal level, but can also cause tissue damage, compromise the integrity of the intestinal barrier and lead to systemic infections when overproduced [181,182]. IL-6 is mediated by the nuclear factor kB (NF-kB), which is involved in the pathogenesis of inflammatory diseases [183]. Bovine colostrum was able to reduce NF-kB activation and, consequently IL-6 production in an *in vitro* model [182]. In another *in vitro* model, colostrum inhibited the NF-kB pathway in human colon cancer HT29 cells, protecting against intestinal epithelial cell inflammation [184]. These results are in agreement with [185], who observed a negative effect of bovine colostrum on the transcriptional activation of NF-kB. Bovine colostrum seems to have a strong capacity to increase the production of some cytokines and decrease others. It also appears to inhibit the production of cytokines that are present in higher concentrations in colostrum than in milk, such as IL-6 and INF-γ, probably as a means of regulating and establishing a balance between exogenous and endogenous cytokine levels.

Complement System

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Colostrum and milk contain various proteins of the complement system [186–188]. It is involved in innate and specific immunity and plays an important role in defending against pathogens. Complement proteins can be activated by the classical pathway, the alternative pathway, and the lectin pathway [186].

It seems that proteins related to the complement system are upregulated in colostrum compared to milk, such as clusterin (clearance of cellular debris and apoptosis in MFGM), complement factor B (related to the alternative pathway of the complement system), C3, C7, and C9 (classical pathway of the complement system) [187,188].

The newborn calf can acquire these proteins from colostrum but complement activity can also be found in the foetal serum and right after birth. For example, C3 was not found in foetal serum and was only detected in calves between 1-3 days old [189]. In contrast, complement activity was not found in lambs at birth, only becoming detectable from day 1 (after colostrum consumption) and increased until day 20 (end of the study) [190]. In this study, there were no differences in the complement activity, IgG, IgM, and chitotriosidase activity between lambs fed colostrum at 2h or 14h post-natal. It has also been shown that the type of milk (goat milk or formula) after the colostrum feeding period can influence the activity of the complement system in goat kids [191]. It is also important to mention that temperature affects the expression of complement proteins (positively and negatively, depending on the proteins) [77,189]. For example, C1, C2, and C8 showed a good heat resistance (56 ºC), C7 showed a moderated resistance and C3 and C6 increased after heating [189].

Classical and lectin pathways are compromised in the newborn calf, but complement-mediated cytotoxic functions normalise between days 7 and 28 after birth [16]. During this period, the incidence of neonatal GIT and respiratory disease is increased, so adequate transfer of immune factors through colostrum is essential to protect the calf while its innate immunity becomes competent. The combination of maternal and innate complement systems helps in the defence against microorganisms during the first days of life, but it is important to note that the effectiveness of the complement system in the GIT of the newborn calf is not clear due to the activity of proteases [186].

In this section (2.3.1.), only those proteins in colostrum with the most scientific evidence that have important biological functions in the newborn calf have been mentioned, but there are many more that have not yet been extensively studied [188]. Colostrum has at least 253 proteins in the whey fraction, of which 36 are uniquely present in colostrum compared to milk. Proteomic analysis of colostrum from different species could provide more knowledge about the factors of variation as well as the role of these proteins in the newborn [77,187,192].

2.3.2. Fatty Acids

Although, the general trend is similar, the lipid profile differs between colostrum, transition milk, and milk [193] (Table 4), highlighting possible specific needs of newborn calves [194]. Colostrum, like milk, is particularly rich in saturated fatty acids (SFA) and monounsaturated fatty acids (MUFA), with a lower proportion of polyunsaturated fatty acids (PUFA) [90,194]. Around 65.6 – 74.1% of the total FA are SFA, 24.5 - 28.4% are MUFA and 3.88 - 4.28% are PUFA [193–195]. Compared to milk, colostrum seems to have a lower content of SFA, branched chain FA, MUFA and conjugated linoleic acid (CLA), but a higher content of PUFA, ω-3, ω-6, and cholesterol (see Supplementary Table S1), and this is more pronounced in the first hours after birth [193–196]. In transitional milk, the lipid profile generally gradually changes to a profile more similar to that found in milk. However, some lipids, such as high carbon number TAG, can maintain their initial concentration beyond the first milking [195]. Nevertheless, there is some variation within each group of FA, phospholipids, and TAG, so a general statement may not be entirely appropriate. There is disagreement in the literature regarding the lipid profile between colostrum and milk, so more research is needed to understand what factors may be involved in the differences observed among studies, such as supplementation during pregnancy, which appears to have a considerable effect [197,198]. There is general agreement that palmitic and oleic acid are the most abundant FA in colostrum, but myristic and stearic acid are also present in higher proportions than the rest of the FA, although stearic acid is present in lower proportions in colostrum compared to milk [90,193,194]. This

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is also true for other species, with the exception of myristic acid [199]. The FA or FA groups present in higher concentrations in colostrum than in transition milk or milk are shown in Table 4.

Linoleic acid (LA) and alpha-linolenic acid (ALA) are essential fatty acids (EFA) [200], classified as n-3 and n-6 FA respectively, they cannot be synthesised by mammals and must therefore be ingested, they are precursors to n-3 and n-6 PUFA, which are essential for metabolic regulation, cell membrane function, and gene regulation [198]. It is not clear whether LA and ALA are more concentrated in colostrum than in milk, but it appears that n-3 and n-6 fatty acids are more concentrated in colostrum (Table 5), but further research is needed to clarify this due to the variability found between studies. Factors that can influence this variability in colostrum are not understood.

It appears that the placenta has different permeability to different FA, for example, supplementation of cows with docosahexaenoic acid or ALA during late gestation affected plasma levels of docosahexaenoic acid but not ALA in calves [201]. EFA and CLA supplementation altered the FA composition of skeletal muscle and adipose tissue in calves [202], and influenced their metabolism [203], growth and feed efficiency [204] via placental, colostral or dietary transfer.

Garcia et al. [205] found that pre-weaned calves supplemented with LA had lower plasma concentrations of acid soluble protein and platelets, higher plasma n-3 FA, glucose, and IGF I, haematocrit and blood lymphocyte concentrations, increased IFN-γ production by peripheral blood mononuclear cells and higher feed efficiency; and that calves from cows supplemented with stearic acid (SFA) before parturition had higher dry matter intake and average daily gain [205], and higher plasma IgG and AEA [197]. Supplementation of cows with PUFA (LA or eicosapentaenoic and docosahexaenoic acid) resulted in higher colostrum IgG concentrations [206], and calves fed colostrum from supplemented cows also had higher plasma IgG levels and higher AEA [207]. The mechanisms underlying this increased IgG uptake are not fully understood. Nevertheless, the authors postulate that could be related to an effect of the FA in the membrane of enterocytes [197], probably at the microvillar membrane, a specialised part in the luminal surface of the membrane, which is a phospholipid bilayer aggregated with specific proteins, although it is important to note that immature cells found in newborns have different functionality [208]. On the other hand, Hiltz and Laarman [209] found that calves fed colostrum replacer supplemented with 2.5% (w/v) butyrate decreased serum IgG concentrations and AEA, which may be related to the ability of butyrate to promote enterocyte differentiation and proliferation, leading to faster maturation and consequent loss of intestinal non-selective absorption capacity, ultimately reducing IgG uptake [209,210].

Calves receiving colostrum supplemented with n-3 FA had increased plasma concentrations of n-3 FA and decreased oxidative stress, but no change in health and growth parameters [211,212], the authors suggest that continuous supplementation rather than one-time supplementation may have altered the results. However, [213] also found no benefit of continuous supplementation with n-3 FA on the health and growth of pre-weaned calves. The growth and immunomodulatory effects in calves vary depending on the type of n-3 FA, the dose and the diet in which they are provided, and may even worsen the outcome [213,214]. Overall, it seems to be beneficial to supplement the dam or calf with FA, but inclusion limits and the lipid source should be considered. However, it is clear that lipids are crucial for the newborn, highlighting the importance of the fat content of colostrum, which is sometimes overlooked in favour of the protein fraction.

Table 4. Predominant trends of fatty acids in colostrum compared to transitional milk or milk.

Fatty acid	Predominant trend
C4:0 Butyric Acid	↓
C6:0 Caproic Acid	↓
C8:0 Octanoic Acid	?
C12:0 Lauric Acid	?
C14:0 Myristic acid	↑
C14:1 ω-5 Myristoleic acid	?
C15:0 pentadecanoic acid	?
C16:0 Palmitic acid	↑
C16:1 ω-7 Palmitoleic	?

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C17:0 Heptadecanoic acid	?
C18:0 Stearic acid	?
C18:1 ω-9 Oleic acid	?
C18:2 ω-6 Linoleic acid (LA)	↑
C18:3 ω-3 α-Linolenic acid (ALA)	?
C21:0 Behenic acid	?
C20:3 ω-6 Dihomo-γ-linolenic acid	?
C23:0 Tricosanoic acid	?
SFA	?
Branched-chain FA	?
MUFA	?
Trans-MUFA	↓
Conjugated linoleic acid (CLA)	↓
PUFA	↑
ω-3	↑
ω-6	↑

↓ indicates that the fatty acid or fatty acid group is present at a lower concentration in colostrum than in transitional milk or milk; ? indicates that the results are inconclusive; only one author has presented results or there is an inconsistency between references; ↑ indicates that the fatty acid or fatty acid group is present at a higher concentration in colostrum than in transitional milk or milk. Based on refs [193–195].

Table 5. Fatty acids present in higher concentration (g.100 g^{-1} total fatty acid) in colostrum compared to milk (at 5th of lactation).

Fatty acid	Colostrum	Milk (5d)
C14:0 Myristic acid	12.8 - 13.7	8.3 – 11.2
C16:0 Palmitic acid	32.5 – 40.4	27.2 – 29.7
C18:2 ω-6 Linoleic acid (LA)	1.95 – 2.79	1.53 – 2.23
PUFA	3.88 - 4.28	2.97 – 3.62
ω-3	0.56 – 1.18	0.33 – 0.70
ω-6	2.57 – 3.72	2.64 – 3.00

Values were obtained from refs [193–195].

2.3.3. Oligosaccharides

Oligosaccharides (OS) are carbohydrates containing three to ten monosaccharides linked by glycosidic bonds and are divided into two classes: neutral and acidic. While the neutral OS does not contain charged carbohydrates residues, acidic OS contain one or more negatively charged residues of sialic acid (the most prominent in bovine colostrum is 5-N-acetylneuraminic) [215]. There have been 52 OS identified in bovine colostrum and milk [216–218], but recently another OS has been found in colostrum [219]. Sialylated oligosaccharides are the major OS in colostrum and milk, representing more than 70% and 50% of the total fraction, respectively [217]. 3′-Sialyllactose (3'SL) and 6′-Sialyllactose (6'SL), 6′-Sialyllactosamine (6'SLN), and Disialyllactose (DSL) are the most abundant in colostrum and are also more concentrated in colostrum than in mature milk, especially 3'SL [220–222] (Table 6).

There are not many studies quantifying OS in bovine colostrum and milk, mainly due to the difficulty of the analytical process [217]. Nevertheless, concentrations of the most abundant OS have been reported [220–225]. OS in bovine milk or colostrum can vary with breed [218,224], parity [222,225], days in lactation [217,222], hours post-partum [220], and heat treatment [223]. As can be seen in Table 6, 3′SL is the most abundant OS in colostrum. There is considerable variation among studies. This may be related to the time of sampling after birth and to individual genetic variation [216,222]. 3′SL was highly affected by heat treatment in comparison to other OS [223] and represents a major source of variation (see Supplementary Table S2).

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Table 6. Most abundant sialylated oligosaccharides in bovine colostrum and milk with corresponding concentrations (mg/L).

Oligosaccharide	Raw colostrum	Mature milk
3′-Sialyllactose (3′SL)	341 - 867	42 - 114
6′-Sialyllactose (6′SL)	103 - 243	17 - 89
6′-Sialyllactosamine (6′SLN)	117 - 239	11 - 170
Disialyllactose (DSL)	84 - 520	4 - 38

Values were obtained from refs [220–225].

Recent research has shown that OS in bovine milk have beneficial effects on neonates in several species. Milk OS may promote gut health by acting as a prebiotic for beneficial bacteria; increase beneficial bacterial colonisation of the surface of epithelial tissues; help defend against infection by acting as a decoy for pathogens, thus inhibiting pathogen adhesion to host target cells; and by being able to modify epithelial glycan receptor expression and also by competitive binding with the host cell surface receptor [226].

In an *in vitro* model, OS were shown to restore intestinal barrier function by promoting the formation of a mucus layer that reduces bacterial adherence, thereby increasing epithelial cell protection, and by reducing damage to the intercellular junction of intestinal epithelial cells [227]. OS ameliorated microbiota dysbiosis and intestinal barrier function in obese mice by increasing the abundance of *Lactobacillus* and reducing intestinal inflammation, as shown by decreased expression of colonic TNF-α [228]. They can promote the growth of beneficial bacteria, which compete with pathogenic bacteria and produce metabolites such as bacteriocins and disrupt the acid-base balance in the gut, inhibiting the growth of pathogens [229]. It has also been shown that OS can also help establish early colonisation of beneficial bacteria, such as *Bifidobacterium*, in the newborn calf gut [223]. Bovine OS may also have an effect at the level of neurological tissues, as it has been shown to improve spatial cognition in premature pigs, with hippocampal upregulation of genes related to sialic acid metabolism, myelination, and ganglioside biosynthesis [230].

Compared to bovine, human colostrum has less protein and fat but more lactose [231]. This may be due to the different brain development between the two species, resulting in human offspring requiring more glucose available for neurological tissue development. Interestingly, the OS content of colostrum is similar in both species, but mature human milk can contain almost twice as much OS as mature bovine milk [232]. This similarity is interesting for infant formulas. Although mammals are able to synthesise sialic acids for incorporation into neurological tissues, the rapid development of the infant may exceed the synthesis capacity, hence the higher concentration in human milk [233]. Elephant milk has similar concentrations of lactose to bovine milk, lower than human milk, but the content of OS is higher than bovine and three times higher than human milk, with a very different profile [234]. OS in primate milk is more complex and diverse than in non-primate animals [233]. To date, only chimpanzees, bonobos and Asian elephants have specific combinations of OS characteristics of the human species [235]. This information highlights the importance of OS in more neurologically advanced species, as well as their importance for neurodevelopment and cognition in neonates [232], but more research is needed to understand the functions of OS in neonates and how different OS interact in different species.

2.3.4. Endocrine Factors

Hormones

Although there has been some considerable research into the hormones present in milk in the decades of the 70's and 90's [236], research into the hormone concentrations in colostrum is limited. Colostrum appears to be more concentrated than milk in androstenedione, estrone, oestradiol, cortisol, cortisone, GnrH, GH, prolactin, TRH, insulin, glucagon, leptin, adiponectin, and motilin than milk, and the opposite is true for parathyroid hormone-related peptide (PTHrP), testosterone, progesterone, rT_3 (Table 7). There are other hormones for which this difference between colostrum

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and milk is not yet clear, such as corticosterone, GHIH, oxytocin, bombesine-like peptide, gastrin-releasing peptide, neurotensin, vasoactive intestinal peptide, calcitonin, melatonin, and erythropoietin. Some hormone concentrations in milk are influenced by the lactation phase, pregnancy status, season, diurnal patterns and physiological state of the animal [237–240], making comparisons with colostrum difficult, and also due to differences between analysis methods [241].

The exact role of these hormones in the neonatal ruminant is not fully understood, but it is known that they can be absorbed into the circulation and that they may contribute to the maturation of the gastrointestinal, endocrine, and immune systems [242]. This is particularly relevant due to the immaturity of the newborn GIT, which allows the passage of these hormones into the circulation and, thus, a systemic effect [63]. They can be found in higher concentrations in colostrum or milk than in maternal blood plasma, highlighting their importance for the offspring [236,241]. However, although leptin concentrations are higher in colostrum than in milk (Table 7), there is no evidence of leptin absorption by the neonatal calf, as occurs in other species, such as rats and humans, where this hormone has systemic effects related to food intake, insulin-dependent glucose metabolism, intestinal maturation, and thermogenesis [92].

Interestingly, some steroid hormones are present in higher concentrations in human colostrum than in bovine colostrum, which could be related to the evolution of the mammalian brain, as they regulate cellular mechanisms such as synapse formation, dendritic arborisation, and cell turnover, and generally contribute to physiological, behavioural, and cognitive functions [243,244]. However, steroid concentrations in foods of animal origin can be of concern, making it important to assess hormone concentrations in bovine colostrum, as it is one of the foods with higher levels of these hormones [245].

These peptides exert many different essential functions in the newborn, such as regulating tissue growth and differentiation (promoting: GH, GH-releasing factor (GRF), IGFs, EGF, TGFα; inhibiting: somatostatin (growth hormone-inhibiting hormone - GHIH), TGF-β); metabolism and calorigenesis (TRH, TSH, T_3 and T_4), energy status and glucose metabolism (insulin, glucagon, adiponectin, glucocorticoids, catecholamines) and blood serum calcium levels (parathormone (PTH), parathyroid hormone-related protein (PHrP) [15,242,246–248].

Neohormones, like oxytocin and relaxin, are present in milk and are involved in the regulation of vital mammalian traits, such as internal fertilisation, pregnancy, and lactation [249]. Milk-derived relaxin (in colostrum) has been shown to influence the development of the neonatal reproductive system in female pigs [250]. The transfer of these bioactive factors, which act as signalling molecules in neonatal tissues, through nursing is known as lactocrine signalling [250,251]. Although relaxin is present in the milk of different species, it appears that the gene encoding ovarian relaxin-2 is deleted in bovine and ovine species [252]. Calcitonin is a hormone produced by the thyroid gland that lowers blood calcium by inhibiting the reabsorption of bone calcium and increasing urinary calcium loss [253]. An inhibiting effect of prolactin release by calcitonin has also been reported [242]. Although calcitonin has been mentioned in many publications to be present in the bovine colostrum [63,139,160,254,255] and milk [236], the authors could not find any research showing its concentrations in cow's colostrum or milk, as opposed to human and rat milk [241,242,256].

Table 7. Reported hormone concentrations in bovine colostrum and milk.

Hormone	Colostrum	Milk	References
Gonadal Hormones			
Androstenedione (ng/ml)	0.18 – 8.36	0.1 – 3.5	[239,244,245,257]
Estrone (E1) (ϱg/mL)	1 300 – 31 070	0.6 – 159	[238,239,244,245,258]
17α-Estradiol (ng/ml)	8.6	0.03	[239,245]
17β-Estradiol (E2) (ϱg/ml)	300 – 7010	0.3 – 14.0	[238,239,244,245,258]
Estriol (E3) (ϱg /mL)	< 3000	9.0 – 31.0	[245,258]
Testosterone (ng/mL)	0.1 – ≈ 1.6	20 – 120	[244,245,257]
Progesterone (ng/mL)	2.62 – 6.46	2.13 – 15.49	[239,244,245]
Adrenal gland hormones			
Corticosterone (ng/mL)	?	2.92 ± 0.26	[259]

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Cortisol (ng/mL)	1.71 – 4.4	0.35 – 1.28	[244,259,260]
Cortisone (ng/mL)	2.16 ± 1.71	0.11 – 0.51	[239,244]
Hypothalamus-Hypophyseal Hormones			
Gonadotropin-releasing hormone (GnRH)[a] (ng/mL)	11.78 ± 0.72	0.5 – 3.0	[261]
Growth hormone (GH)[b] (ng/mL)	0.17 – 1.4	< 0.03 – < 1.0	[11,262–264]
Growth hormone-inhibiting hormone (GHIH)[c] (ϱM)	?	19.0 ± 6.0	[265]
Oxytocin (ϱg/mL)	?	8.0 – 10.0	[266]
Prolactin (ng/mL)	280 – 800	3.7 – 57.0	[11,267–269]
Thyrotropin-releasing hormone (TRH) (ng/mL)	0.16 ± 0.03	0.05	[261]
Brain-Gut Hormones			
Bombesin-like (related to gastrin releasing peptide) (ng/mL)	?	1.17 ± 0.89	[270]
Gastrin releasing peptide (nM)	?	1.4 ± 1.0	[265]
Neurotensin	?	?	
Vasoactive intestinal peptide (ϱM)	?	16 ± 9.0	[265]
Pancreatic hormones			
Insulin (ng/mL)	35.4 – 65	1.0	[11,271]
Glucagon (ng/mL)	0.16	0.01	[11]
Thyroid Gland Hormones			
Calcitonin	?	?	
Triiodothyronine (T_3) (ng/mL)	< 0.31 – 2.02	0.21 – 0.41	[262,272–274]
Reverse Triiodothyronine (rT_3) (ng/mL)	0.57 ± 0.06	3.48 – 91.1	[273,274]
Thyroxin T_4 (ng/mL)	0.12 – 1.9	0 – 0.67	[262,272–275]
Other hormones			
Parathyroid hormone-related protein (PTHrP) (ng/mL)	26.0 – 56.0	59.0 – 168.0	[276,277]
Glucagon (ng/mL)	≤ 0.16	0.01	[11,263]
Relaxin	-	-	
Melatonin (ϱg/ml)	?	4.71 - 41.94	[240,278]
Erythropoietin	?	?	
Leptin (ng/ml)	13.9 – 30	4.4 – 6.1	[237,279]
Adiponectin (µg/ml)	56.1 to 75.9	0.61	[280,281]
Motilin (ng/ml)	0.23 ± 0.06	0.03 ± 0.02	[282]

Values refer to mean values reported in research papers. [a] Also referred as Luteinizing hormone-releasing hormone (LH- RH) [b] Also referred as Somatotropin [c] Also referred as Somatostatin.

Growth Factors

After immunoglobulins, growth factors are probably the most studied BC in the bovine colostrum [2,54,100,264,283–286]. There are about 50 different polypeptides that can modulate the growth, maturation and function of the GIT [11,22,287]. Insulin-like growth factor (IGF) 1 (IGF-I) and 2 (IGF-II), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), β-cellulin (BTC), fibroblast growth factor 1 and 2 (FGF1 and FGF2), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) are probably the most important growth factors in colostrum [7,287–289]. See Baumrucker and Macrina [269] for cow colostrum and milk concentrations. Growth factors have a certain degree of thermal tolerance, since they can withstand temperatures up to 60ºC during 30 min [264] or 60 min [290]. However, the need for caution when heat-treating colostrum is reinforced, as to the authors' knowledge there is no information beyond these ranges. These factors also need to survive digestion, retain biological activity, have receptors at GIT or be absorbed, to influence the neonate. The GIT has site-specific receptors in different regions, so it is expected that bioactive components in colostrum will have different effects in different regions of the GIT [140]. The epithelial cells have a high turnover rate and IGFs are key regulators of cell growth and differentiation [291].

Compared to human colostrum, bovine colostrum is particularly high in IGFs and low in components of the EGF family [140]. EGF binds to the epidermal growth factor receptor (EGFR),

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which increases intracellular tyrosine kinase activity, activating signalling cascades that ultimately promote cell proliferation and angiogenesis, and reduces apoptosis [292]. Other EGFR related ligands are TGF- β and BTC [140]. TGF- β is associated with immunomodulatory activities, inflammatory responses, oncogenesis, and proliferation of intestinal cells [22,289,293]. IGFs concentration is also higher in colostrum than in blood [140]. The IGF system is composed by IGFs and IGF binding proteins (IGFBPs) [283]. IGFs are synthesised in the liver in response to the growth hormone (GH) [294] and some IGFBPs are synthesised in the lactocytes of the mammary gland [295]. IGFs and IGFBPs are highly concentrated in pre-partum secretions and colostrum, and decline rapidly in subsequent milkings [11]. While EGF may be more important in the human and porcine species, it can be postulated that IGFs are more important for the ruminant neonate, as they are present in higher concentrations in colostrum [283]. Nevertheless, the neonate calf is also capable of synthetising IGFs in different tissues [140]. The components of the IGF system have different regulatory properties in GIT epithelial cells, IGF-I appears to be more involved in mitogenesis, which promotes enterocyte proliferation and regeneration, and IGF-II may be more related with enterocyte differentiation promoting functions [291].

Delaying colostrum feeding can negatively affect some metabolic and endocrine traits of the newborn. Calves fed colostrum on day 1 had increased circulating glucose, albumin, insulin and IGF-I concentrations compared with calves fed on day 2 of life [296]. Fischer-Tlustos et al. [297] showed that calves fed colostrum right after birth (0h) had an increased GIT development, in terms of some histomorphological parameters like villi height, crypt depth, and surface area index, compared to calves fed 12h after birth, at 51h of age. Smaller differences were observed when compared to calves fed 6h after birth. However, there were no differences in the serum IGF-I concentrations of calves with respect to feeding time, but it was 29% higher at 48h than at 0h after birth (312.8 ± 14.85 vs. 241.9 ± 14.06 ng/mL) [297]. On the other hand, extending colostrum feeding can promote GIT maturation, but similar results can also be obtained with a mixture of colostrum and whole milk (1:1) [298], which has a composition similar to transition milk. Even after gut closure and with theoretically increased proteolytic activity, calves fed colostrum or a mixture of colostrum and whole milk had greater surface area of the GIT, increased villi height in the proximal and distal jejunum than calves fed whole milk, and ileal crypts tended to proliferate more with a mixture of colostrum and whole milk than with whole milk alone, but crypt depth did not differ [298]. However, calves fed colostrum had only minimally increased plasma GLP-2 and serum IGF-1 compared to calves fed whole milk, which the authors believe may be related to inadequate nutrient intake [298]. In an *in vitro* study it was showed that amino acid deficiency reduced intestinal epithelial cell reconstitution through a decrease in TGF-β production [299]. The maternal diet during gestation can also affect the GIT development of the newborn, as lambs from ewes supplemented with folic acid during pregnancy were shown to have increased IGF-I expression, small intestine weight/live body weight ratio, and intestinal muscularis thickness [300]. In fact, growth factors present in colostrum may be able to influence the neonate's growth performance until later in life. A study by Buranakarl et al. [301] showed that kids fed colostrum with higher concentrations of IGF-I (>518.3 ng/ml) had increased body weight gain at the end of the first month than kids fed colostrum with lower concentration of IGF-I (≤518.3 ng/ml). Unfortunately, milk composition was not analysed, since it could have affected the kid's development. It is important to note that IGFs are not the only molecules intervening in the intestinal development, as it is a combination of several bioactive components [283].

2.3.5. Nucleic Acids

MicroRNA

A review on microRNA (miRNA) in bovine colostrum has recently been published [13], and this is a very new area of study within the colostrum field; therefore, we will only briefly describe these molecules on colostrum and milk, and some recent studies on their effect on the newborn calf. MiRNAs are a group of small (18-25 nucleotides in length) endogenously expressed, non-coding RNA molecules, that act as regulators of gene expression and other cell-related regulatory functions,

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like survival, proliferation, apoptosis, tumour growth, and metastasis [302,303]. It has also been shown that miRNAs can act as regulators in many immunological pathways [12,304], in wound healing, and in infection processes [305,306]. Other non-coding RNA molecules include transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) [307].

It is suggested that miRNAs are produced in the mammary gland and transferred to milk and colostrum [137,308,309], protected within extracellular vesicles (EV), such as exosomes. Colostrum seems to have a higher concentration and expression of different miRNAs molecules than transition milk and milk [137,310,311] and some novel miRNA are still being discovered [308,312]. EV are cell-secreted membrane-encased vesicles that contain proteins, miRNA, mRNA, and lipids, depending on their source and are associated with various physiological and pathophysiological processes [306,313]. This allows miRNA to be resistant to acidic conditions (pH 2 at 37ºC for 1h) and to RNases [310], making them resistant to the GIT environment and allowing absorption in the small intestine [13]. This finding contributes to the theory that miRNAs in colostrum and milk act as signalling molecules between the mother and the offspring [13]. However, according to Hue et al. [309], the miRNA present in the newborn calf's bloodstream are not colostrum-derived, but rather from an endogenous source. The study by Kirchner et al. [313] also did not confirm that the miRNAs present in the EV of colostrum either entered the circulation of the newborn calf, remained in the intestinal epithelium, or were rapidly transported to other tissues and were therefore not present in the bloodstream at the time of analysis. These results do not indicate that miRNA from colostrum is absorbed by the newborn calf.

Depending on the phase of lactation, different miRNA may be expressed [13], it seems that during the colostral phase there are predominantly expressed miRNAs associated with immune pathways, while during the rest of the lactation miRNA expressed are more related to milk synthesis [308,314]. Colostrum is also more concentrated in miRNA than transition and mature milk [311]. The same applies to breed differences; compared to beef heifers, the mammary gland of dairy heifers had a more pronounced downregulation of miRNAs involved in the inhibition of genes related to the maintenance and activity of mammary stem cells, presumably required for intensive regenerative processes during puberty and pregnancy [315]. While there are miRNAs that are commonly expressed in colostrum and milk of different species, like miR-30a-5p, miR-22-3p and miR-26a, which are related to immune functions, there is also a significative variation between species [316]. It was found that miRNA abundance was not affected by heat treatment at 60ºC for 60 min, and that miRNA was higher in frozen samples than in raw samples [311].

Some miRNAs have a higher expression level in BC than in milk, such as miR-142-5p, miR-150, miR-155, miR-181a, and miR-223 [137,309]. Ma et al. [317] found that colostrum with very different IgG levels (62.8 ± 3.6 and 256.5 ± 5.7 mg/mL) had a similar expression profile of miRNAs present in small EV, which contributes to the statement that a colostrum with a higher concentration of IgG does not necessarily indicate higher concentrations of the many other BC reviewed in the present article. Nevertheless, studies correlating IgG and other BC are still lacking. Only one miRNA was more abundant in high-IgG colostrum - miR-27a-3p – which is associated with osteogenic differentiation in pre-osteoblasts [317] and with glycaemic and lipid status in women with gestational diabetes mellitus [318].

The importance of miRNAs to the newborn health is clear, and it is also clear that these molecules are highly expressed in colostrum, however it is not clear if their action is dependent on uptake into the bloodstream or if they may act at in GIT. In any case, it seems that they can act as regulators of the mucosal immune system [319] which reinforces their importance has immune modulators of GIT.

Nucleotides and Nucleosides

Nucleotides are monomers that constitute the basic building blocks of nucleic acids (RNA and DNA). They consist of a nitrogenous base, a pentose sugar, and a phosphate group. Nucleosides are essentially nucleotides without the phosphate group. Nucleobases are the nitrogenous bases that are the basic units of the genetic code (adenine (A), cytosine (C), guanine (G), thymine (T), and uracil

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(U)). They are essential for cellular function, acting as mediators of chemical energy transfer, signal transduction and growth regulators [320,321].

Nucleos(t)ides are present in milk and colostrum in the sub milligram per litre range and belong to the non-protein nitrogen (NPN) fraction [322]. The concentration of these compounds shows little variability during lactation, except during the first few days [322,323]. Immediately after birth, the concentration of nucleotides in colostrum is low, but rises to a maximum 24-48 hours later and then gradually decreases [324,325]. Nucleosides are generally found at lower concentrations in milk than nucleotides. They are found in higher concentrations in colostrum, without a clear maximum, and generally decrease to a constant level by 3 weeks after parturition [323]. Uridine and uridine 5′-monophosphate (5′UMP) are the most abundant nucleos(t)ide in colostrum, with concentrations ranging from 50.6-102.4 and 13.33-143.7 μmol/dL, respectively [324,325]. Concentrations and variations during lactation are species-specific, e.g., uridine levels in ewe's milk can be 4 times higher than in cow's and goat's milk at about 24 hours post-partum [324]. Orotic acid is present in much higher concentrations in cow's milk compared to ewe's and goat's milk and appears to increase during the first 2 months of lactation [324]. Gill et al. [321] found a difference in the total base concentration (nucleotides and nucleosides) in colostrum collected in summer and winter (62.1 ± 6.2 and 258.7 ± 6.8 μmol/dL, respectively), with a notable difference between the concentration of 5′UMP in summer (1.2 ± 0.0 μmol/dL) and winter (143.7 ± 8.5 μmol/dL). There is still very little information on the variation of nucleos(t)ides in ruminant's colostrum, and there seems to be a significant effect of species, breed, season, and analytical methods on the differences obtained so far [321,323–325].

Nucleotides, especially those with an uracil nucleobase, contribute to the calf's biological functions. Mashiko et al. [326] showed that a supplementation with 2 g/d of 5′UMP had a positive effect on the immune status of calves aged 4-42 days. In Katoh et al. [327] it was observed an effect of 2 g/d of 5′UMP on the endocrine status of calves 4-14 days old. Oral administration of 5 g of a nucleotide supplement (5'CMP, 5'UMP, 5'AMP, and 5'GMP) improved growth performance, intestinal morphology, and oxidative status in pre-weaned calves [328]. Supplementation of sows with uridine and cytidine (Ur:Cy = 1:1) reduced birth mortality, increased piglet birth weight, and modulated gene and protein expression of enzymes involved in lipid metabolism in the liver of neonatal piglets [329]. Maternal supplementation with yeast-based nucleotide containing 5′UMP increased litter weaning weight and decreased diarrhoea rate, promoted ileal villus development, increased secretory IgA in the ileum and jejunal, and increased jejunal and ileal expression of interleukin IL-17, IL-8, IL-1β, IL-10, and TNF-α in piglets [330]. However, in another study where sows were supplemented with a yeast-based nucleotide without 5'UMP, there was no effect on sow or piglet performance [331]. Including 10 and 20% of a nucleotide mixture (NuPro, Alltech Inc., Nicholasville, KY) in the milk replacer formula of male calves worsened growth performance and did not improve health status [332]. Feeding calves a yeast-based nucleotide mixture (NuPro, Alltech Inc., Nicholasville, KY) resulted in improved intestinal function and morphology, but feeding purified nucleotides (80 μmol/L of AMP, 64 μmol/L of CMP, and 374 μmol/L of UMP) did not, and resulted in lower faecal beneficial bacteria, higher harmful bacteria, faecal water loss and calf dehydration [333]. A reduction in *Lactobacillus* spp. was also observed in calves supplemented with nucleotides (yeast-derived; 500 g/t of milk replacer; Ascogen, Chemoforma, Switzerland) [334]. Most studies on nucleotide supplementation have tested pre-weaned calves, but it appears that post-weaning nucleotide supplementation may result in better growth performance [335,336]. It may be of interest to study the effect of nucleotide supplementation, especially uracil-based, in the very first days of life, given the good results of maternal supplementation and the natural variation of nucleos(t)ide in bovine colostrum.

2.4. Cells

The cell fraction of colostrum can be divided into: epithelial cells (lactocytes), erythrocytes, and leukocytes [9,136]. The mammary gland's epithelial cells contribute to the host defence, by expressing pathogen recognition receptors (e.g. toll-like receptors) and synthesising proteins with antimicrobial properties such as lactoferrin, β-defensin, and lipopolysaccharide binding protein [9]. Epithelial cells

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are present in the bovine colostrum at 2 to 15% of the total cell count [337]. In contrast, epithelial cells make up more than 20% of the total cell count in sow colostrum [8]. The leukocyte fraction consists mainly of lymphocytes, macrophages, and neutrophils and its concentration depends on diet, age, breed, and physiological and individual conditions [8,337,338]. For example, it has been shown that heifers have lower activity of colostral immune cells than cows with 3 or more lactations [339]. On the other hand, Kampen et al. [340] found no significant effect of the cow health status on colostral lymphocyte concentration. In Park et al. [341] colostrum collected 48h before and after parturition differed in the percentage of leukocytes, with an increase in all subpopulations except macrophages, which increased, suggesting a decrease in leukocyte count with the onset of lactation, similar to other components in the BC; however, only 2 cows were sampled in the 48 h prepartum period. In contrast, in pigs, the percentage of T lymphocytes, B lymphocytes and macrophage/monocyte subsets in colostrum did not differ between 0 and 8h postpartum [342].

Colostrum contains approximately 10^6 leukocytes/mL, and macrophages and neutrophils are the major fractions of colostral cells, followed by lymphocytes (Table 8) [311,337,341,343]. In the lymphocyte fraction, the T lymphocytes represent a higher proportion of the total cell count than B lymphocytes, 16 and 10.7% respectively [341,343,344]. Although these proportions appear to be consistent across studies, there is still considerable variation in the number of cells. The total cell count, usually referred to as the somatic cell count (SCC) of colostrum, is around 2.3×10^5 and 5×10^5 cells/ml [338,343], but can range from 1.2×10^5 to 1.9×10^6 cells/mL [85,345]. The specific influence of factors in these variations is not entirely understood.

Table 8. Mean variation in the differential leukocyte count (%) in bovine colostrum and milk.

Leukocytes differential count	Colostrum[a]	Milk[b]*
Lymphocytes (total)	2 – 27	18 - 58
Lymphocytes T	16	47
Lymphocytes B	11	20
Macrophages	31 – 69	10 – 29
Neutrophils	30 - 65	28 - 49

[a] Values were obtained from refs [311,337,341,343]; [b] Values were obtained from refs [346–348]; * Includes results from dairy cows in various stages of lactation.

Significant effects of freezing and heat treatment on colostral cell viability have been reported. The rapid freezing of colostrum in liquid nitrogen, followed by a slow thawing, resulted in a lysis of the cells, which led to an inability to detect these cells under the microscope [349]. Rapid freezing of colostrum on steel plates pre-cooled to -80 ºC followed by heat treatment at 50 ºC also resulted in cell lysis [350]. Similarly, no percentage of viable cells was found in pooled colostrum frozen at -20 ºC for a period between 24 h and 3 months and then thawed (37 ºC) prior to administration, in contrast to fresh colostrum which had 24 ± 8% viable cells [351]. Similar results were found in Chandler et al. [311] with no viable cells after freezing at -20 ºC overnight or heat treatment (60 ˚C for 60 min), but there were more than 80% viable cells in fresh colostrum cooled on ice and stored at 4 ˚C overnight. In contrast, frozen (-20 ºC) porcine colostrum had reduced numbers of lymphocytes (CD79a+) and conventional B cells (SWC7+CD5-), but not macrophages, granulocytes, and NK cells [342]. Similarly, feeding fresh or frozen colostrum did not significantly affect the neutrophil and monocyte activation in newborn dairy calves [352]. Heat treatment (60 ºC for 60 min) reduced the SCC of bovine colostrum by 36% [286]. Martínez et al. [353] studied the effect of different treatments on the SCC of ewe's milk analysed by the Fossomatic method and concluded that freezing milk at -20 ºC only reduced the SCC when azidiol was used as a preservative and when the milk was heated to 60 °C, whereas unpreserved milk or milk preserved with bronopol or potassium dichromate and analysed at 40°C did not affect the SCC. Significant differences in SCC between fresh and frozen BC were also not found in another study [42]. It can be assumed that freezing may cause cell lysis, but they can still be counted in the Fossomatic method, as according to [311] intact (but not viable) cells and cell components are still visible after freezing. Freezing and heating may therefore affect cell viability in colostrum.

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Leukocytes are absorbed by the intestinal epithelium of the newborn, allowing them to migrate to Peyer's patches and mesenteric lymph nodes, or to enter the systemic circulation and eventually reach other organs associated with the immune system, such as the liver and spleen, normally within 24h after colostrum ingestion [337,354,355]. To be absorbed, leukocytes must undergo phenotypic changes provided by the colostrum environment in the mammary gland [355].

In the swine species, there is a maternal-neonatal recognition that does not allow the passage of colostral cells or peripheral blood leukocytes from other sows through the piglet's intestinal wall [8], but it does occur in primates [356] and sheep [357], and probably in cows, although this is not clear as in most studies calves were fed colostrum from their respective dams. It is important to identify this issue as many farmers feed calves with colostrum from a colostrum bank, rather than from the dam. Nonetheless, in one study where calves were fed pooled colostrum or colostrum from another dam, passive immune transfer, morbidity, and weaning weight did not differ from calves fed maternal colostrum [358].

At birth, the newborn calf has a naive innate immune system; a deficient and immunosuppressive state is evidenced by increased expression of TGF-β1 and TGF-β2, together with reduced functions of phagocytosis and platelet aggregation [16]. Thus, immunocompetent colostral cells (as well as immunoglobulins and other immune factors present in colostrum) are necessary to induce cell-mediated responses and to enhance both innate and adaptive responses.

It is likely that maternal leukocytes migrate to different tissues depending on their ability to express the CD62L receptor. Leukocytes with little or no expression of CD26L are likely to migrate to peripheral non-lymphoid tissues where they act as memory cells; leukocytes expressing higher levels of CD26L expression are more likely to migrate to secondary lymphoid tissues where they can act as regulators of the newborn's specific immune responses [355]. In fact, memory activated T cell phenotypes are the most common in colostrum [8,355].

Maternal colostral cells allow more rapid development of adaptive immunity by enhancing the antigen presenting capacity of monocytes and lymphocytes, as indicated by increased expression of MHC class I molecules [359,360]. Maternal colostral cells also have a long-term effect on the development of the calf's immune system, improving responses to vaccines [361]. Maternal vaccination may improve neonatal defences against certain pathogens, as transfer of antigen-specific lymphocytes through colostrum can occur with antigens to which the dam has been exposed [337,350], but there are still few studies in bovine species on maternal-neonatal transfer of antigen-specific immunity.

Colostrum affects the B cell lineage of the newborn calf [362]. Exposure to maternal commensal microbes in utero or spontaneous production of low affinity natural antibodies causes a calf that has not received colostrum to have IgG positive cells in the lymphoid tissues, whereas calves fed colostrum do not [362]. This occurs because the colostral immune system can suppress or eliminate IgG-positive B cells but does not affect IgM- and IgA-positive cells in the mesenteric lymph nodes, which may play an important role in mucosal immunity in the early life of the calf [362]. The BC also has a much higher concentration of IgG than IgM and IgA, which may also contribute to this suppression of neonatal IgG production, but not IgM and IgA. This phenomenon may be necessary for transferring maternal components (which would otherwise be foreign to the neonate), which also results in prolonged tolerance to maternal immunoglobulins, increasing their longevity during the development of the innate and acquired immune systems [362].

2.5. Microorganisms

Feeding colostrum increases gut bacterial colonisation in the newborn calf [363]. Bacteria can reach the cow's mammary gland exogenously, specifically from the maternal skin, or endogenously with an immune-related translocation of intestinal bacteria to the mammary gland, referred to as the entero-mammary pathway [364]. The former can explain the presence of aerobic microorganisms and the latter the presence of anaerobic microorganisms in colostrum or milk. It is hypothesised that the aim of this process is to 'train' or 'educate' the newborn's immune system to recognise commensal microorganisms and develop an appropriate response [364].

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The microbial quality of colostrum is usually assessed using total plate count (TPC) and total coliform count (TCC), which provides an overall assessment of hygiene conditions from milking to feeding. It is difficult to establish a mean value for the TPC of BC because there is a large variation between published studies. Mean TPC in raw colostrum can range from 250,000 [365] to 1062 ufc/mL [366] ufc/mL,. Mean TCC can range from 12 ufc/mL [42] to 63,000 ufc/mL [351]. Elevated TPC and TCC are associated with colostrum contamination. Current targets are a TPC below 100,000 cfu/mL and a TCC below 10,000 cfu/mL [367]. While coliforms are essentially faecal bacteria, that can include *E. coli*, TPC includes a wide variety of bacteria, including beneficial bacteria. Therefore, a higher TPC should not necessarily indicate poorer microbial quality. Other recommendations from the same reference include streptococci and staphylococci below 50,000 cfu/mL [367].

Heat treatment of colostrum is aimed at reducing pathogenic bacteria. It was found that heating colostrum at 60 ºC for 60 or 120 min reduced TPC and pathogenic bacteria without affecting IgG concentration [7,368]. Other combinations of time and temperature above 60 ºC resulted in a significant loss of IgG concentrations [7,368]. Heat treatment can effectively reduce TPC and TCC, but staphylococci appear to be more resistant to heat treatment [286].

Colostrum also contains beneficial bacteria, like lactic acid bacteria (LAB), but current recommendations are based only on pathogenic bacteria. While heat treatment significantly reduces TPC and TCC [286,365], there is still a gap in the knowledge of the interaction between beneficial and pathogenic bacteria in raw, frozen, and heat-treated colostrum. Using quantitative real-time PCR analysis, detectable bacteria were only present in untreated colostrum samples, from which *E. coli* represented 70.6% of the total bacteria, whereas no bacteria were detected in heat-treated (60 °C/60 min) samples, but it was shown that calves fed heat-treated colostrum 6 h after birth had higher intestinal colonisation with *Bifidobacterium* [363]. In another study, a significant reduction in LAB (lactococci and lactobacilli) counts was found when heat treatment (treatment 1 – 56 °C/60 min or treatment 2 – 63 °C/30 min) was applied to raw caprine colostrum [369]. In contrast, LAB isolated from colostrum showed good *in vitro* antimicrobial activities and antioxidant power [370]. LAB supplementation improved body weight gain, feed conversion, and faecal condition in calves [371,372]. While pathogenic bacteria can reduce IgG absorption in the neonatal gut by binding to bacteria or by competing for epithelial receptors, the role of beneficial bacteria in this process is not well understood [373].

Culture-independent microbiome studies have shown that the BC microbiota is dominated by four phyla: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria [14,373–375]. The top 10 genera in BC are listed in Table 9. Of these 10 genera, *Acinetobacter*, *Pseudomonas* and *Staphylococcus* are the most frequent in the BC. Factors such as season, breed [373], parity [14], antibiotics' administration [376], and mastitis [14] can affect the colostrum microbiota. At the phylum level, colostrum core microbiome is relatively stable, at the genus level there is some variation that is not fully understood, and at the species level there is a considerable variation [374].

Table 9. Cores microbiome of colostrum (genus level) according to the frequency that a certain genus has been considered part of the colostrum core microbiome in literature.

Genus	Phyla	Frequency
Acinetobacter	Proteobacteria	+++++
Pseudomonas	Proteobacteria	++++
Staphylococcus	Firmicutes	++++
Bacteroides	Bacteroidetes	+++
Corynebacterium	Actinobacteria	+++
Streptococcus	Firmicutes	+++
Bacillus	Firmicutes	++
Chryseobacterium	Bacteroidetes	++
Flavobacterium	Bacteroidetes	++
Lactococcus	Firmicutes	++

In terms of inclusion criteria, the genera had to be designated as colostrum core or top genera in at least two studies. The symbol "+" indicates the number of studies. Values were obtained from refs [14,373,374,376,377].

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The genus *Acinetobacter* comprises more than 50 Gram-negative coccobacilli species from which the majority are non-pathogenic environmental organisms [378]. *A. baumannii* is the best known species of this genus and has clinical significance in both human and veterinary medicine, as it can be associated with different types of infections in different species and due to its ability to accumulate antimicrobial resistance [379]. Patangia et al. [376] has confirmed this, has *Acinetobacter* had a high abundance in the colostrum of the cows that received antibiotics as part of the dry therapy. They are common in the environment and are therefore likely to be present in the cow's GIT, allowing them to migrate into colostrum, but it is not yet understood whether they have a specific role in the mammary gland or in the GIT of the neonate, as they are commonly abundant in different studies.

Pseudomonas and *Staphylococcus* can also be pathogenic and appear to be positively correlated in colostrum, as well as *Chryseobacterium* [374]. In contrast, they were negatively correlated with the *Bacteroidales-S24-7-group*, which are beneficial bacteria [374]. There also appears to be a relationship between the concentration of IgG and the prevalence of certain microorganisms in colostrum. For example, the genera *Lactococcus* and *Carnobacterium* (beneficial bacteria) were more abundant in colostrum with an IgG concentration above 100 g/L than in colostrum with an IgG concentration below 50 g/L [373]. In contrast, a species of the *Enterobacteriaceae* family (coliforms) was 97 more abundant in colostrum with an IgG concentration of less than 50 g/L than in colostrum with a higher IgG concentration (> 50 g/L) [373]. It is not yet understood whether IgG is lower or higher depending on the microbiome, or the opposite, but it seems plausible that a combination of both may occur. Lima et al. [14] found that bacteria with a pathogenic tendency were more abundant in the colostrum of multiparous cows than primiparous cows, and that primiparous cows had a richer microbiota, but primiparous cows with lower diversity may be more susceptible to future disease events. These findings highlight the importance that the microbiome in colostrum and milk may have on mammary gland defence and consequently on the calf's mucosal defence. Calves fed milk replacers instead of milk (from healthy cows) do not benefit from this training and defence provided by the colostrum microbiome, so the inclusion of probiotics may help to alleviate this deficit.

Like the colostrum microbiota, at birth the calf's GIT is dominated by Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes, which is similar to the in-utero microbiota, but it can change rapidly, within 24h the calf's GIT can be colonised by pathogenic bacteria such as *Escherichia Shigella*, *Clostridium spp.*, and *Enterococcus spp.* [380]. This is particularly likely if colostrum administration is delayed [381]. From the results obtained by Malmuthuge et al. [363], calves are born with a low bacterial density but with a high proportion of beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, compared to potentially pathogenic bacteria, such as *E. coli*. However, colostrum can modulate this microbiome, and in this study, providing colostrum reduced the intestinal *Lactobacillus* content, but when colostrum was heat-treated (60 °C/60 min), the prevalence of *Bifidobacterium* was higher at 6h postnatal compared to untreated colostrum or no colostrum groups; however, at 12h postnatal there were no differences in *Bifidobacterium* prevalence between the groups of calves that received colostrum. In addition, calves that did not receive colostrum had higher levels of *E. coli* at 6h and 12h after birth than calves fed colostrum, especially when compared to calves fed heat-treated colostrum [363]. This confirms that environmental bacteria can colonise the calf's gut very quickly and highlights the importance of providing good quality (chemically and microbiologically) colostrum soon after birth. During the first few days, the microbiota of calves continues to change and is related to the calf's health status [377]. At 14 days of age, there were differences in the faecal microbiome between healthy and diarrhoeal calves, with a high prevalence of *Faecalibacterium* and *Butyricicoccus* species in healthy calves [377]. Colostrum and milk microbiome, in combination with the environment, modulate the GIT microbiome of calves; however, this area of study is relatively new and warrants further investigation.

3. Conclusions

There is a vast quantity of research on the IgG variation and concentrations on the bovine colostrum, and to some extent in major components like protein and fat. However, research on minor components is less clear, being affected by analytical methods and possibly other uncontrolled factors, resulting in greater variation in the values reported in the literature. Research on these compounds *in*

vivo using larger animal models such as ruminants, horses, and pigs is very limited, and there are still many generalisations made from laboratory animals, *in vitro* models and, in some cases, human infants. The quality of colostrum is usually assessed by the concentration of IgG, but the importance of other components for the newborn is now clear. However, the degree of proportionality between IgG and other components is not fully understood. Evidence suggests a beneficial effect of consuming maternal colostrum rather than colostrum from another dam, but for practical reasons, calves usually receive colostrum from a colostrum bank. This beneficial effect is mostly related with immune cells viability and possible with specific maternal-offspring signalling molecules. The concentration of certain compounds is significantly higher in colostrum than in milk, which may indicate a specific value for the newborn. As morbidity and mortality increased in the early days of life, research into these compounds and the maternal-neonatal recognition effect could improve calf health and welfare. This opens opportunities for research as colostrum can be used not only for the newborn but also as a nutraceutical and therapy for animals and humans. Future areas of study may focus on colostrum proteomics and metabolomics, oligosaccharides such as 3'-sialyllactose, fatty acids, immune cells, and the microbiome. This research suggests that there is still much to learn about colostrum synthesis and its ability to improve the quality of life of farmed and non-farmed animals.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Table S1: Qualitative comparison of lipid content between colostrum and either transitional or mature milk; Table S2: Most abundant sialylated oligosaccharides in bovine colostrum and corresponding concentrations (mg/L). Mean values from each reference are shown, as well as a calculated mean, standard deviation (SD), and coefficient of variation (CV).

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