Non-Bovine Milk and Milk Products

Edited by
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CHAPTER

4

Influence of Animal Health, Breed, and Diet on Non-cow Milk Composition

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1. INTRODUCTION

Non-cow milk is the predominant source of nutritious food in many parts of the world. Buffalo milk serves as a significant source of milk in developing countries, particularly in India. Goat milk is estimated to be a small contribution to the world's milk production, but this is misleading since it is concentrated in developing countries (East Asia, Africa, and South America) where smallholders' units provide essential food to local consumers. Thus it is likely that the number of people consuming goat milk is even larger than those using cow milk (Silanikove et al., 2010, 2015). In addition, although non-cow milk prevails in developing countries, it should also be considered that small ruminants' milk from goats and sheep is a major staple of traditional foods (mainly in the form of cheese and yogurt) in many modern and developed western countries (Silanikove et al., 2010). In countries such as Spain, France, Greece, and Italy, cheeses made from sheep and goat milk are often categorized as protected designation of origin (PDO) and are considered as gourmet food receiving the highest prices among cheeses available on the market. In other parts of the world humans consume milk from local mammals as camels, yaks, and donkeys.

It is well established that the chemical composition of milk is substantially affected by many factors, such as species, breed, stage of lactation, animal's age, health, feeding regime, and season (Alston-Mills, 1995; Chilliard and Ferlay, 2004; Jenkins and McGuire, 2006). However, the most controllable factor in dairy farming responsible for reduced milk quantity and quality is intramammary infection (IMI). In the current review, we focus on factors affecting milk quality in the short range, mainly animal health and more specifically udder infection by bacteria, because they have immediate impact on milk quality both from industrial perspectives (Silanikove et al., 2014a) and food safety for humans (Silanikove et al., 2010, 2014b; Leitner et al., 2015).

Currently, global milk production is dominated by five animal species: dairy cattle, buffalo, goats, sheep, and camels. According to the Food and Agriculture Organization of the United Nations (FAOSTAT, 2013) for the year 2009, the world's total milk production accounted for 696.6×10^6 tons, of which 83.3% (580.5×10^6 tons)

Non-Bovine Milk and Milk Products
http://dx.doi.org/10.1016/B978-0-12-803361-6.00004-1

was cow milk, 13% (90.3×10^6 tons) buffalo milk, 2.2% (15.1×10^6 tons) goat milk, 1.3% (9×10^6 tons) sheep milk, and 0.2% (1.6×10^6 tons) camel milk. The major cow milk producers worldwide are the European Union (148.1×10^6 tons), the United States (85.9×10^6 tons), India (~45×10^6 tons), and Russia (32.3×10^6 tons). The production of buffalo milk is concentrated in two countries. Nearly 92% of its worldwide production is in India (60.9×10^6 tons) and Pakistan (21×10^6 tons). The largest producers of goat milk in the world are India (26.3%) and Bangladesh (14.3%), and leaders among the European countries are France (3.8%) and Greece (3.3%). The world's major producer of sheep milk is China (12.2%). The leaders in Europe include Greece (8.7%), Turkey (8.2%), Romania (7.2%), and Italy (6.1%). Camel milk is almost exclusively produced in Somalia (54.4%), Ethiopia (11.9%), Mali (8.1%), Sudan (7.5%), and Saudi Arabia (5.6%).

Goat milk constitutes only 2.1% of global milk production, ie, approximately 15×10^6 tons, but is relatively significant in sub-Saharan Africa, and parts of South Asia and of East and South-East Asia, excluding China, where it accounts for ~10% of the total (Gerosa and Skoet, 2012). Taking into account that goats are considered as poor men's cows and prevail in most farms in South Asia and of East and South-East Asia, it is likely that goat milk is the major source of dairy food, providing essential supply of protein, energy, and minerals to the large population in those areas (Silanikove et al., 2010). Europe produces only 2.5% of the world's goat milk, but it is the only continent where goat milk production has significant economic importance and organization.

2. OUTLINE OF THE MAJOR FEATURES OF NON-COW MILK-PRODUCING ANIMALS

The available information on milk composition of non-cow milk is considerably less than that available for cow milk. However, between non-cow species, relatively much more is known about goat and sheep milk composition. Therefore the major features of goat and sheep milk are briefly outlined here.

2.1 Goat (*Capra Aegagrus Hircus*)

The gross milk composition of goat and cow milk is similar, but a closer look unveils many advantages of goat over cow milk from a nutritional point of view. The most prominent features include smaller milk fat globules and casein micelles allowing better digestion; a higher proportion of fatty acids with health benefits; casein composition closer to human casein composition associated with lower allergenicity, better availability, and utilization of major (calcium) and minor (iron) minerals; and much higher concentration of various minor components with health-promoting properties. Goat milk fat has high levels of caproic, caprylic, and capric acid with low amounts of butyric acid (Haenlein, 2004; Park, 1990, 1991, 1994; Park et al., 1986, 2007; Silanikove et al., 2010).

2.2 Sheep (*Ovis Orientalis Aries*)

Sheep milk contains higher levels of total solids (protein and fat) and more major nutrients than goat and cow milk. Sheep milk has higher casein content and larger casein micelle size, which affect their renneting properties and coagulation time. The higher casein content of casein, which functions as a chelator of divalent (or higher valence) ions, is associated with higher content of those mineral contents than in cow, camel, and goat milk. The average fat globule size is smallest (<3.5 μm) in sheep milk followed by goat and cow milk. The yield of curd and cheese per volume of milk is the highest among ruminant milk. The higher casein content and plasmin activity in sheep makes them more sensitive than goats to bacterial infections, which is reflected in higher reduction in milk yield and poorer clotting capacity compared to goats (see discussion below for the physiological basis) (Anifantakis, 1986; Park et al., 2007; Silanikove et al., 2010).

2.3 Water Buffalo (*Bubalus Bubalis*)

The water buffalo, also known as the domestic Asian water buffalo, is a large bovid that has been raised since its domestication in South Asia, South-East Asia, and China, and today it is also found in Europe (mainly Italy), Australia, and some American countries (Cockrill, 1977). The wild water buffalo (*Bubalus arnee*) native to South-East Asia is considered a different species, but likely is an ancestor of the domestic water buffalo (Lau et al., 1998). There are two subtypes of water buffalo, distinguished on the basis of morphological and behavioral criteria: the river buffalo of South Asia, which is found in the Balkans, Egypt, and Italy, and the swamp buffalo, found in Assam in the West through South-East Asia to the Yangtze valley of China in the East (Cockrill, 1977). Based on phylogenetic studies, it has been suggested that the swamp type may have originated in China and was domesticated ~4000 years ago (Table 4.1), whereas the river type may have originated in India and was domesticated ~5000 years ago (Yang et al., 2008). There has been little exchange of cross-breeding buffaloes among countries; therefore, each population within a given country has its own phenotypic features and performance (Moioli and Borghese, 2005). Water buffalo milk contains higher levels of total solids, crude protein, fat, calcium, phosphorus, and slightly higher content of lactose compared to cow milk. The high level of total solids makes water buffalo milk ideal for processing into value added dairy products, such as butter and cheese.

TABLE 4.1 Approximate Dates and Locations of Dairy Species Domestication (Rossel et al., 2008; Silanikove et al., 2015)

Species	Time	Location
Sheep (*Ovis orientalis aries*)	Between 11,000 BCE[a] and 9000 BCE	Mesopotamia
Goat (*Capra aegagrus hircus*)	8000 BCE	Mesopotamia
Cow (*Bos primigenius taurus*)	10,800–10,200 BCE	Mesopotamia
Water buffalo (*Bubalus bubalis*)	5000–7000 BCE	India, China
Yak (*Bos grunniens*)	4500 BCE	Tibet
Donkey (*Equus africanus asinus*)	5000 BCE	Egypt

[a] *BCE: Before the Common Era.*

2.4 Yak (*Bos Grunniens*)

The yak belongs to the bovine subfamily, which was domesticated around 7000 BC (Table 4.1). Yak is raised in high-altitude areas characterized by extremely cold (as low as −40°C) and low atmospheric pressure (550 hPa). The total world yak population is approximately 14.2 million (Wiener et al., 2003). Domestic yaks graze throughout the highlands of the Hindu Kush and Karakoram in Afghanistan and Pakistan; the Himalayas in India, Nepal, and Bhutan; the Tibetan Plateau and Tian Shan Mountains of Northern China, Western and Northern Mongolia; and also in some areas of Russia and former USSR countries in Asia. China has the largest number of yaks in the world with approximately 13 million or >90% of all the world's yaks. Yak milk yield of 147–487 kg per lactation has been reported (Neupaney et al., 1997). Yak milk and dairy products are popular foods in high-altitude regions. The milk contains 16.9–17.7% solids, 4.9–5.3% protein, 5.5–7.2% fat, 4.5–5.0% lactose, and 0.8–0.9% minerals. Yak milk contains much lower fat in summer than in winter, which is in part due to the greater summer milk yield. While the milk yield is not very different between the first and second lactation, milk fat is much higher during the second lactation. Yak milk is often used for cheese-making, known as "chhurpi" in Tibetan and Nepali languages and "byaslag" in Mongolian. Yak milk butter is used to make "butter tea" in Tibet. Although not widely available in regions such as North America, yak dairy products and particularly yak cheese are becoming more accessible in dairy markets. Yak cheese contains about four times more linoleic acid than Canadian cheddar, with increased human health implications (Neupaney et al., 1997). It is richer in protein, casein, and fat than cow milk. High contents of colloidal and soluble calcium and phosphorus are other advantages that make highly suitable for cheese-making. The milk fat of yak at very high altitudes is richer in polyunsaturated fatty acid (PUFA) and conjugated linoleic acid (CLA).

2.5 Camel (*Camelus*)

Camels are the most adapted desert-dwelling domesticated ungulates. There are two types of domesticated camels: the single-humped dromedary (*Camelus dromedarius*), which has been domesticated in the Arab peninsula ~3000 BC (Spassov and Stoytchev, 2004), and the double-humped Bactrian (*Camelus bactrianus*), which was domesticated in the cold desert region of China and Mongolia ~5000–6000 BC (Ji et al., 2009; Table 4.1). As of 2010, there were around 14 million camels, with 90% being dromedaries (FAOSTAT, 2013). Dromedaries are herded mostly in the Horn of Africa, the Sahel, Maghreb, Middle East, and South Asia, whereas the Bactrian inhabit the Gobi Desert in China and Mongolia. The Horn region alone, particularly in Ethiopia and Somalia, has the largest population of camels in the world. Camel milk is a staple food for desert nomad tribes and in rough periods, such as during continuous years of drought (Silanikove, 2000a) or during long journeys in the desert, where it plays an essential role in survival. Camel milk is rich in vitamins, minerals, proteins, and immunoglobulins (Shamsia, 2009) and compared to cow milk, it has lower amounts of fat and lactose and higher amounts of potassium, iron, and vitamin C (Konuspayeva et al., 2009; https://en.wikipedia.org/wiki/Camel - cite_note-camello-10). Camel milk is less readily converted into butter, cheese, and yogurt, but is known for its health-promoting properties and a lot of research has been performed to explore and characterize these properties (Sharma and Singh, 2014). Thus studies such as this may result in increasing use of camel milk for medicinal food and camel milk-derived nutraceuticals.

2.6 Donkey (Jenny, Jennet; ie, Female Donkey; *Equus Africanus Asinus*)

The donkey or ass is a domesticated member of the horse family, Equidae. The donkey has been used as a working animal for at least 5000 years (Table 4.1). There are more than 40 million donkeys in the world, mostly in developing countries, where they are used principally as draught or pack animals. In the last decade, however, there has been an increase in donkeys being raised as dairy animals. Donkey milk is similar to mare milk and human breast milk as it is relatively poor in protein and fat but rich in lactose. The casein-to-whey protein ratio is intermediate between human milk and cow milk. Consequently, donkey milk is considered to be the closest to human breast milk. Recent studies have shown that ass milk could serve as an alternative to cow milk for children allergic to bovine proteins (Guo et al., 2007). Ass milk has been considered since Hippocrates (460–370 BC) to possess medicinal properties (Adams, 1859). There is a lot of contemporary research on the medicinal and cosmetic properties of donkey milk, but it is used mostly as a source of hypoallergic milk (Guo et al., 2007).

3. ANIMAL HEALTH, BREED, DIET, AND ENVIRONMENTAL EFFECTS

The long-term effects on milk composition are dependent on genetics, species, breed, and the individual animal. In the previous section, the main features of each of the main dairy species were considered; in this section the effect of breed, diet, and animal health are briefly considered. Each of these elements represent a very broad aspect; therefore, we limit our discussion to the basic aspects with an emphasis on modern aspects, such as adaptation of dairy farm management to modern life and those resulting from ongoing and expected changes of climatic changes and its impact on the dairy industry.

3.1 General Characteristics of Dairy Species

Fat and protein content generally increase or decrease in parallel, but fat varies more with feed and season than protein. The fat, solids-not-fat, and protein contents of milk are high in early lactation, fall relatively rapidly at the beginning of lactation, reach a minimum toward the peak of lactation, and then increase steadily, reaching maximal concentration toward the end of lactation. These trends cause an inverse relationship between the yield of milk and the concentration of these components and affect cheese-yield ripening and flavor (Jenkins and McGuire, 2006). Generally, less roughage and more high-energy feeds support higher milk yield and lower fat content with little decrease in protein content (Jenkins and McGuire, 2006).

While the above-described general principles are applicable to all dairy species, they vary within species (eg, lactation and pregnancy length) and breed according to evolutional history and dietary habits. Buffaloes are grazers that evolved in tropical environments and thus their nutritional demand is similar to tropical cattle (*Bos indigus*); they utilize highly fibrous feed better than temperate origin cattle (*Bos taurus*) (Bhatia et al., 1998). Goats and camels are browsers with a very efficient digestive capacity that enables them to eat fibrous plants that are rich in secondary metabolites, such as tannins (Silanikove, 2000a). Goats and camels are thus the most flexible and opportunistic domestic animals in diet selection and foraging behavior. There is a close interrelationship between abundance of given plant species in a grazing area and their ratio in goat and camel diet. Thus the dietary choices of goats and camels are much broader than those of sheep and cattle grazing in the same area (Elmi et al., 1992; Migoncobake et al., 1987; Silanikove, 2000a).

3.2 Interactions Among Breeds, Environment, and Health

Hundreds of goat and sheep breeds are raised in different geographical locations around the world (Porter and Masson, 2002). In general, there are more dairy breeds of goats than dairy breeds of sheep. Some dairy goat breeds, particularly those selected for temperate environments, such as Sannen, Alpine, and Toggenburg, are chosen for their high milk yield (500–to 3000 L/lactation), which on metabolic weight basis is equivalent to the production of high-yielding modern dairy cows. The vast majority of breeds have also been selected for centuries for management and environmental conditions in particular geographical zones. The anglo-Nubian breed is an example of combining the adaptive features of goats to hot environments with selection toward high milk yield.

The environment, within which dairy production, agricultural crops, and related management practices developed over the past 10,000 years, is rapidly changing due to human-induced climate change (CC) (Silanikove and Koluman, 2015). Today, even countries located within temperate zones are affected by global warming. The rate of global warming, including in temperate zones, is expected to continue to increase. Agricultural production from crops and livestock, and thus global food security, is already affected by CC and will continue to be influenced by global warming. Thus these changes will continue to directly and indirectly affect the dairy industry. The most significant indirect effect is expected to result in the reduction of worldwide grains (concentrate feedstuff) production. This change will create the need to use higher proportions of grain production for human nutrition instead of feeding it to livestock (Silanikove and Koluman, 2015). Heat stress (Table 4.2) imposed by high ambient temperature in temperate zones, such as in Germany, Northern Italy, and the United States, has been identified in recent years as a major factor that negatively affects milk production, reproduction, and the health of dairy cows. Heat stress has also been shown to increase cow mortality in those areas. On the other hand, there is no evidence that dairy goat production in temperate zones has been affected thus far, despite some evidence existing for the dessert and the Mediterranean countries.

Among domestic dairy species, goats and camels are the most adapted to heat stress in terms of production, reproduction, and resistance to disease. Thus CC is expected to negatively affect the dairy industry and thus the importance of goats and camels to the dairy industry will increase in proportion to the changes in the environment. In fact, there is statistical evidence that suggests that this trend is already occurring. The number of dairy camels was two-fold greater in 2009 than in 1961, compared with 2.13-fold for buffaloes (mainly in India), 2.52-fold for goats, and only 1.43-fold for cattle, with the growth in sheep population being the lowest (1.08-fold) (FAO, 2012). The increase in dairy goat production is not restricted to developing countries in harsh environments, but has also been seen during the last decade in the Mediterranean zone of developed countries, such as France (3.4% increase) and especially Spain, where the number of goats has increased by 8.8% (Castel et al., 2010). In some countries, namely, Greece, Albania, and some of the central and eastern European countries, such as Bulgaria, Bosnia, Herzegovina, Croatia, and Slovenia, the contribution of goats and sheep to dairy production is sizable, around 40%, and in some countries (eg, Greece), the contribution exceeds that of cows (Silanikove and Koluman, 2015). This is due, in part, to the ability of goats to uniquely and effectively exploit the vast scrub and wood land that characterize those countries (Silanikove, 2000a), which may eventually be the dairy industry structure in other zones (Silanikove and Koluman, 2015).

TABLE 4.2 Comparison of Weather Heat Stress Risk Classes Between Dairy Goats and Dairy Cows (Silanikove and Koluman, 2015)

Heat stress class	Dairy cows	Dairy goats
Normal: No effect on milk yield	THI[a] < 74	THI < 80
Alert: Modest effect on milk yield	74 ≤ THI < 79	80 ≤ THI < 85
Danger: Severe effect on milk yield	79 ≤ THI < 84	85 ≤ THI < 90
Extreme: Can result in death	THI ≥ 84	THI ≥ 90

[a] *THI: Temperature Humidity Index.*

4. MASTITIS

In this chapter we focus on factors affecting milk quality in the short range, mainly animal health and specifically udder infection by bacteria, which is the most important single factor affecting milk quality (Leitner et al., 2011a; Silanikove et al., 2014c). Mastitis is an intra-mammary inflammation of one or more of the udder glands that is caused mainly by penetration of a variety of bacteria into the gland through the teat canal. If a pathogen is isolated from the milk it is then called intramammary infection (IMI). The inflammation is usually accompanied by physical, chemical, and pathological changes in the mammary tissue and is characterized by an increase in the number of somatic cells in the milk, ie immune cells from the blood and epithelial cells from the mammary tissue (International Dairy Federation, 1987; Kelly et al., 2011). Mastitis can be clinical, which includes acute signs of infection (ie, fever, edema, pain and/or hardness, and a major increase in somatic cells count (SCC) of up to several millions per mL milk), or sub-clinical, which at most times is overlooked due to the lack of acute signs and a moderate increase in SCC. Thus the SCC serve as a guideline for milk hygiene and milk quality, although most of the data related to this subject deals with dairy cows.

Based on the numerous data available for dairy cows, a quarter producing milk with $>100\times10^3$ cells/mL is defined as sub-clinically inflamed by bacteria, while bacteriologically negative quarters with $<100\times10^3$ cells/mL are considered as healthy (Pyörälä, 2003; Ruegg and Pantoja, 2013). However, these numbers can change moderately in healthy animals, depending on breed, age, stage in lactation, season, milking frequency, etc. (Silanikove et al., 2010).

Regarding buffalo, in a study performed in Sri Lanka, it was found that total SCC in normal buffalo milk varied from 50×10^3 to 375×10^3 cells/mL (Silva and Silva, 1994). However, data on buffalo milk SCC are limited, which leads to uncertainty about the level of SCC in buffalo milk that can be used to determine the presence of inflammation (Ceron-Munoz et al., 2002; Dhakal et al., 1992; Mahendra and Ludri, 2001; Pasquini et al., 2003). However, recent reports suggest that in buffalo, as in dairy cows, SCC is a valid indicator of udder inflammation (Tripaldi et al., 2010). Previous studies have shown that after the first 90 days of lactation, the level of somatic cells increases progressively and that days in milk and parity also have a significant influence on SCC (Ceron-Munoz et al., 2002). A later study by Piccinini et al. (2006) confirmed these findings with an increasing frequency of quarters in the high SCC range ($>400\times10^3$ cells/mL) as parturition and days in milk progressed. Information on bacteria-causing mastitis is available. Osman et al. (2009), Salvador et al. (2012), and Mustafa et al. (2013) reported similar causative agents and prevalence as in cows; however, much more information is needed to support these data. As in other dairy animals, elevated SCC impairs milk coagulation properties and milk quality (Tripaldi et al., 2003).

Camel is another non-cow species on which relatively more information, compared to yak and donkey, on the effect of IMI on milk yield, milk hygiene, and immune response at the level of the mammary gland, exists (Obied et al., 1996; Hamed et al., 2010, 2012; Nagy et al., 2013). Though qualitatively immune responses to bacterial infections, such as increase in SCC and increase in the number of neutrophils, are similar to equivalent responses in bovines (Obied et al., 1996; Nagy et al., 2013), three features appear to be unique to camels: (1) similarly to goat, camels seem to have low levels of plasminogen in milk (Hamed et al., 2012). The plasminogen-plasmin system plays an important role in regulating milk secretion through plasmin-derived casein degradation products (Silanikove et al., 2010). The conversion of plasminogen to plasmin is regulated by plasminogen activators. The activity of plasminogen activators and their inhibitors depends on hormonal signals in the systemic circulation and the activity of plasminogen activators, which increases under stressful conditions (Silanikove et al., 2006). The low concentration of plasminogen in camel milk at all times strongly suggests that milk secretion in camels is less affected by stresses such as dehydration and heat that frequently prevail in their environment (see Fig. 4.1 for illustration of mechanism). (2) Camel milk has higher proportions of lymphocytes and macrophages than cow milk at equivalent conditions (at high SCC level as a result of infection and at mid-to-late lactation), which suggests that the innate and acquired immune systems of camels are different from those of cows, which may relate to their capacity to resist stress and infections (Hamed et al., 2010). (3) Camel milk has a high basal level of *N*-acetyl-*β*-D-glucosaminidase (Chaffer et al., 2000), similar to the phylogenetic relative llama as well as in human milk, in which the activity of this enzyme is ~20-fold higher than in

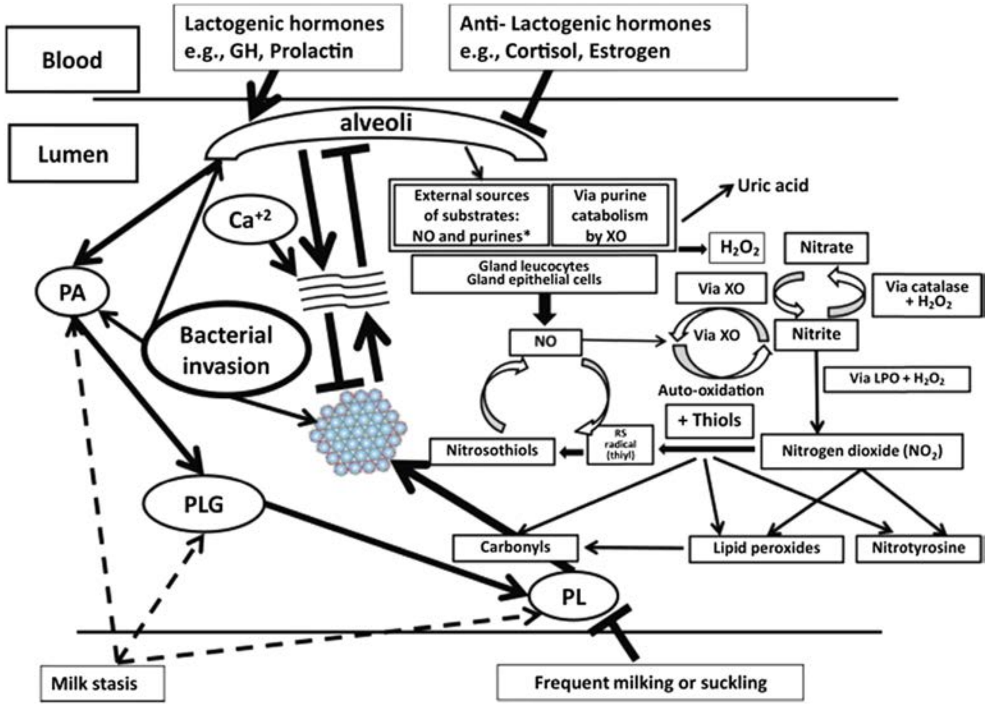

FIGURE 4.1 Schematic model that describes the simultaneous activation of the plasmin (PL) system and the nitric oxide (NO)-derived cycle in sub-clinically infected mammary glands. The increased activity of PL causes release of peptides from the casein micelles, which in turn down-regulates milk secretion and casein micelle clotting (Leitner et al., 2011a). The release of peptides rich in phosphates impairs the coagulation of milk by reducing Ca^{+2} availability (Fleminger et al., 2013). In parallel, the pro-inflammatory peptides released by PL up-regulate the NO-cycle rate in milk. The increased release of NO into milk is associated with upregulation of formation of bactericide radical (nitric dioxide), which is associated with formation of nitrotyrosine, carbonyls, and lipid peroxide (Silanikove et al., 2005, 2009). Hydrogen peroxide plays an important role in the NO cycle as a substrate for lactoperoxidase in forming nitric dioxide and as a substrate for catalase in conversion of nitrite to nitrate. The latter reaction is the main mechanism that restrains the NO cycle in milk. The source of hydrogen peroxide in milk is oxidation of xanthine and hypoxanthine by xanthine oxidoreductase, which results in accumulation of uric acid as the end product of the xanthenes oxidation (Silanikove et al., 2005, 2009, 2012). The increased content of oxidized components in milk most likely increases their susceptibility to proteolysis of milk proteins (Leitner et al., 2006). Explanation of symbols and abbreviations used in the figure: Casein-derived active peptides: , casein micelle: , CAT = catalase, LPO = lactoperoxidase, NO = nitric oxide; PA = plasminogen activator, PL = plasmin, PLG = plasminogen, XO = xanthine oxidoreductase. *From: Silanikove, N., Merin, U., Leitner, G., 2014a. On effects of subclinical mastitis and stage of lactation on milk quality in goats. Small Ruminant Research 122, 76–82.*

non-infected cow milk (Silanikove et al., 2006). In cow and small ruminants, the basal level of *N*-acetyl-*β*-D-glucosaminidase is much lower than in camels and its activity correlates with SCC, making it a sensitive indicator of mammary gland inflammation (Kitchen et al., 1984; Vihan, 1989; Maisi, 1990; Berning and Shook, 1992; Leitner et al., 2001, 2003; Pyörälä, 2003). *N*-acetyl-*β*-D-glucosaminidase is a lysosomal enzyme that confers antimicrobial activity (Silanikove et al., 2006). Thus the high basal content of *N*-acetyl-*β*-D-glucosaminidase in camel milk is consistent with the conclusion that the innate immune system of camels differs from that of other ruminants, which may explain its high natural resistance to bacterial infections.

The main difference between sheep and goats relates to higher fat and protein content and higher activity of the plasmin system in sheep milk. Because of the higher content of casein and fat, the yield of curd and cheese per liter of milk is the highest among dairy animals (Park et al., 2007). However, because of the higher activity of the plasmin system, which increases during subclinical infection, and because of the higher casein content, which is the substrate of plasmin activity, sheep are more sensitive than goats to subclinical infection (Silanikove et al., 2010; Fig. 4.1). This is reflected by the higher reduction of milk and curd yield in sheep than in goat when exposed to the same infection despite having similar SCC (Leitner et al., 2004a,b,c). Two recent examples demonstrate the negative effect of subclinical mastitis on the quality of fresh and mature sheep cheese (Rovai et al., 2015a,b).

4.1 Effects of Subclinical IMI and End of Lactation on Milk Yield and Quality

The first step in producing cheese is curdling of the milk. In milk from uninfected mammary glands, curd yield mainly depends on the content and subtypes of α_{S1}-, β-, and κ-caseins (Hyslop, 2003; Vazquez-Flores et al., 2012; Mestawet et al., 2014), fat level, and protein-to-fat ratio (Guinee et al., 2007). Phosphoseryl residue on α_{S1}- and β-caseins are bound in the micelle to polyvalent cations, which are mostly Ca^{+2} ions. Exposition of the phosphoseryl residue due to the activity of the clotting enzyme leads to charge neutralization, aggregation, and eventually to precipitation and formation of the curd matrix. During aggregation, casein forms a fine mesh that entraps the fat globules and leaves the soluble lactose in the whey. Thus the main components of curd are the casein and minerals associated with it, most notably Ca^{+2}, fat, and components attached to the milk fat globule membranes, such as fat-soluble vitamins.

Cheese is prepared by utilizing a wide range of microbial cultures responsible for the development of a variety of aromas and flavors. In combination with maturation conditions and time periods, an impressive range of cheeses varieties, each with its own unique taste, shape, color, texture, and rheological properties, are produced worldwide. Recently, it was shown that cheese made from the milk of IMI glands negatively affects the chemical processes that occur during cheese maturation. Despite the fact that the curd mass of cheese made from milk taken from uninfected glands was equal to the curd mass of cheese made from milk taken from infected glands, the final product from milk from the infected glands had lower yield and quality (Albenzio et al., 2002; Merin et al., 2008; Le Maréchal et al., 2011; Marti-De Olives et al., 2011; Giadinis et al., 2012; Gonzalo et al., 2012; Rovai et al., 2015a, b).

4.2 Experimental Models Used to Investigate the Effects of IMI

The half-udder model, in which a single gland serves as the experimental unit and the contralateral gland as a control, has been used extensively by our research group (Leitner et al., 2004a,c,d, 2006, 2008a,b, 2011a) and also by others (González-Rodríguez et al., 1995; Martí-De Olives et al., 2013) to study the effect of IMI on milk yield and milk quality. This experimental model enables the study of the physiological basis and quantification of the negative effects of IMI on milk yield and quality with high statistical reliability, even for relatively small data sets of 20–40 animals. The half-udder model is an effective tool for isolating the experimental effects from numerous masking effects. The experimental variability was due to significant individual variations between individual animals and was further complicated by the effects of factors, such as farm management, environmental conditions, animal husbandry, age, and stage of lactation. Obviously, variations caused by all of these factors are neutralized when the units of comparison are the two glands of the same animal. An alternative approach based on conventional whole-udder sampling would have required a data set of the order of 100 animals to account for the large above-described sources of variability (Leitner et al., 2004b). However, because of the tendency of the uninfected gland to compensate for the reduction in milk yield of the infected gland and because such compensation is not possible when both glands are infected, the effect of IMI on the whole-animal level was found to be larger than that obtained by the average effect found with the half-udder model (Leitner et al., 2008a). Thus for the purpose of quantifying the effect of subclinical IMI on a whole-herd level, especially in herds with poor hygiene, it is preferable to conduct experiments that include milk sampling of all the goats in a given flock and to combine this information with information gained by the half-udder model (Leitner et al., 2004b, 2007).

4.3 Bacteria and the Etiology of Infection

Worldwide, IMI in small ruminants (sheep and goats) and large ruminants (cows) is a major cause of economic loss to the dairy industry. Effective control of new IMI cases and consequently, milk yield and milk quality, including SCC in the milk of dairy animals is aided by understanding of the pathogens involved, the source of infection, and the frequency of natural cures (Lam et al., 1997; Leitner et al., 2007).

In goats, as in sheep and cows, subclinical mastitis is the prevalent form of IMI (Bergonier et al., 2003; Leitner et al., 2004b,c; 2007). The prevalence of subclinical mastitis in small ruminants could be as low as 5% under very good husbandry conditions, but typically, it affects 15–40% of the animals in a given flock. On the other hand, annual incidence of clinical mastitis is generally lower than 5–10% (Contreras et al., 2007; Silanikove et al., 2010). Staphylococci, such as *Staphylococcus aureus* and coagulase-negative staphylococci (CNS), are the frequent pathogens isolated from IMI goats (Contreras et al., 1999, 2007; Leitner et al., 2004b). However, CNS, mainly *Staphylococcus caprae*, *Staphylococcus epidermidis*, *Staphylococcus chromogenes*, and *Staphylococcus simulans*, comprise the most abundant bacterial isolates that dominate the bacteria isolated from IMI in goats in almost all flocks tested in different parts of the world (Kalogridou-Vassiliadou et al., 1992; Contreras et al., 1999, 2007; Leitner et al., 2001, 2003, 2004a,c,d, 2007, 2008a, 2011b; Foschino et al., 2002; Moroni et al., 2005; Silanikove et al., 2010; Souza et al., 2012; Rovai et al., 2014).

Characterizing the etiology of bacterial infection is important for understanding the grounds for establishing infection and devising appropriate treatments to control the contagion. However, very little research has been performed to explore the IMI-acquiring patterns in goats. The only study we are aware of in which the etiology of IMI was systemically analyzed was that of Leitner et al. (2007), which comprised a survey of three goat flocks in Israel. It was found that ~15% of the yearling does were already infected with bacteria when they joined the flock, whereas ~8% of the goats that dried-off with no infection returned with new IMI. Virtually, none of the goats acquired infection during lactation. Thus the etiology of IMI in goats was found to be very similar to that of dairy cows (Leitner et al., 2008b), which leads us to believe that this study represents a genuine description of IMI spread in goats. The study by Leitner et al. (2007) contradicted the common view that prevailed before 2007, but was never sustained by experimental evidence, that goats acquire bacterial infection during milking throughout lactation. The results suggest that, as in cows, preventive measures against acquiring IMI need to be concentrated on applying effective dry-off treatment and on preventing the stress of parturition or in early identification of animals that would resist such stress (Leitner et al., 2008b). However, we are aware of only a few efforts to use antibiotics for dry-off treatment in goats and sheep, and the results regarding the efficiencies of those treatments are contradictive (Poutrel et al., 1997; Mavrogianni et al., 2004; Contreras et al., 2007; Leitner et al., 2007; Shwimmer et al., 2008).

4.4 Use of SCC for Predicting Losses of Milk and Curd Yield

An inflammatory response that increased SCC was studied in individual animals with IMI, mainly with CNS (Contreras et al., 1999; Leitner et al., 2004a). The inflammatory response is associated with the reduction in milk yield in the infected glands compared to that of the uninfected ones, as found in sheep and cows (Leitner et al., 2004a, 2006, 2011a; Martí-De Olives et al., 2013; Fig. 4.1). In sheep, the reduction in milk yield is much more significant when both glands are infected than when only one gland is infected. When only one gland is infected, the contralateral gland yield increase compensates for the reduction in the infected gland. However, in sheep the compensation is smaller than that in goats (Leitner et al., 2008a).

Extensive field studies in France (Baudry et al., 1997), Spain (Contreras et al., 2007), Israel (Leitner et al., 2007), and the United States (Barrón-Bravo et al., 2013) leave no doubt that on the farm level increased SCC is associated with IMI and reduced milk yield compared to farms with low SCC. The exploitation of utilizing SCC to predict reduction in milk and curd yield is considered in the following. By applying the half-udder model, it was shown that curd yield was significantly lower in infected halves than in uninfected ones, although casein content was almost equal in the two glands (Leitner et al., 2004a,c; 2011a). In a study of Manchega and Lacaune dairy sheep breeds, a significantly higher SCC was found in the infected glands of both breeds, and, thus, 25–30% of the milk from the infected glands did not coagulate. In comparison to samples taken from contra-lateral uninfected glands, the rennet-clotting time of milk from infected glands was twice as long and curd firmness was lower. Blending milk from uninfected and infected glands resulted in different coagulation properties of the milk, in its syneresis, and in a softer and more elastic texture of the produced cheese. The study showed that a high proportion of milk from infected glands influenced uninfected milk and was responsible for the above changes. In addition to the influence of IMI on milk and cheese quality, storing of such milk caused further deterioration of its quality, which was pronounced as lower yield and quality in Manchego cheese (Rovai et al., 2015a,b; Abdelgawad et al., 2016).

Similar negative effects of IMI on curd and cheese, which are not associated with casein content, were also reported for cow milk (Auldist and Hubble, 1998; Leitner et al., 2006; Merin et al., 2008). Thus these data indicate that knowledge of the gross casein and fat content of milk is insufficient for predicting curd yield in milk affected by the presence of bacteria in the mammary gland lumen. The potential biochemical reasons for that are discussed below.

Although there is a clear trend showing the inverse relationship between high SCC and milk yield or milk quality, using the SCC level for such predictions is complicated. Somatic cells are a mixture of different types of leukocytes, neutrophils, macrophage, and T-cells, in addition to epithelial cells (Leitner et al., 2011b, 2012). While any kind of bacterial infection will result in increased SCC in milk, the level of the increase of SCC sub-types is unique to the kind of bacteria, time after infection occurrence, and species involved, because it depends on the specific interactions between the invader and host immune system (Leitner et al., 2006, 2012). Some bacteria species such as *Streptococcus dysgalactiae* and *Escherichia coli* are much more devastating in terms of their effect on milk quality. However, impairment of milk quality in cows infected by those bacteria was not well predicted by an increase in SCC. Deterioration of milk quality in IMI cows was found to be directly related to liberation of peptides with anti-clotting properties from casein, to changes in casein micelle that impaired clotting (Merin et al., 2008; Fleminger et al., 2011, 2013), and to the level of imposition of oxidative stress on milk proteins (Silanikove et al., 2007, 2014d). The effects on milk quality described above were studied in cow milk. A recent study shows that the same effects are relevant to goats, although goat milk quality is less affected by IMI than bovines (Silanikove et al., 2014a,d).

However, despite these limitations and in view of the ease of measuring SCC routinely, it seems that it is still possible to use SCC as a criterion for milk quality as discussed below. A scheme to grade milk according to the level of SCC in goats was proposed by Leitner et al. (2008a, 2015). In deriving the scheme, we considered the following factors: (1) prevalence of CNS as the causative agent of subclinical IMI in goats, (2) subtypes of CNS interacting similarly with the immune system and thus causing similar increase of SCC, and (3) information gained from a series of studies on infection within individual animals at both the herd and gland level. Care was taken to ensure that when data from whole animals were used it did not relate to the first week of lactation and to data gathered after 180 days in milk. These restrictions were applied in order to reduce as much as possible the confounding effects discussed above, particularly the effect of stage of lactation. Recommendations on how goat and sheep milk should be graded are presented in Table 4.3. To the best of our knowledge, this is the only scheme that provides recommendations on how to grade goat milk for industrial use. The data clearly indicate that the loss of curd yield is greater than the loss of milk yield.

A recent wide survey covered data from several years and was based on monitoring SCC and milk yield in the United States. It was concluded that high SCC may be associated with up to a 30% reduction in milk yield compared to milk yield in goats with low SCC (Barrón-Bravo et al., 2013). However, in this study no effort was made to isolate the effect of IMI, thus it may reflect the above-discussed confounding effects; in particular, the combination of end of lactation and IMI is expected to be influential, which may explain the great gap between the two latter predictions.

According to the propositions made by Leitner et al. (2008a), goat and sheep milk with >3,500,000 cells/mL should not be accepted for marketing because of (1) the high probability that such milk will contain pathogens and toxins; (2) its poor industrial quality, very low or complete absence of curdling; and (3) the potential formation of toxic radical substances in the milk (Silanikove et al., 2012, 2014a).

TABLE 4.3 Calculated Herd Milk Loss and Curd Loss in Sheep and Goat Due to Infection Level (Leitner et al., 2008a,b)

Infection level	Projected SCC	Milk loss (%)	Curd loss (%)
Sheep			
Grade A: 0–25%	450,000–800,000	0–4.1	0–5.2
Grade B: 25–50%	800,000–1,400,000	4.1–8.2	5.2–10.4
Grade C: 50–75%	1,400,000–2,000,000	8.2–12.2	10.4–15.5
Goats			
Grade A: 0–25%	250,000–840,000	0–0.8	0–3.3
Grade B: 25–50%	840,000–1,200,000	0.8–1.5	3.3–6.5
Grade C: 50–75%	1,200,000–1,600,000	1.5–2.3	6.5–9.8

5. PHYSIOLOGICAL AND BIOCHEMICAL BASIS FOR THE EFFECTS OF SUBCLINICAL MASTITIS AND LATE LACTATION ON MILK YIELD AND QUALITY

5.1 Effect of Subclinical Mastitis

Subclinical mastitis is typically a chronic situation in which a compromise between the inability of the host to eradicate the bacteria and restriction of the pathogen presence to the mammary gland, where there is no threat to the life of the organism (Leitner et al., 2011a). The immunological interactions of the host with CNS that cause subclinical IMI in goats in comparison to sheep and cows were recently described (Leitner et al., 2012).

The physiological basis for the decline in quality of milk from IMI glands was extensively studied by our group (Shamay et al., 2002, 2003; Leitner et al., 2004a,c, 2008a, 2011a, 2012; Silanikove et al., 2005, 2006, 2009, 2010, 2014a,b). These studies, in agreement with previous ones, highlighted the role of the plasmin system in downregulation of milk yield and breaking casein micelles during IMI (Bastian and Brown, 1996; Politis, 1996). An updated version of negative-feedback regulation based on the plasmin system activity is presented in Fig. 4.1.

According to this model, enzymatic hydrolysis of casein by plasmin liberates peptides that serve as local regulators of mammary gland functions. In particular, a peptide that is formed by the activity of plasmin on β-casein, namely β-casein *f*(1–28), which down-regulates milk secretion in cows and goats. β-casein *f*(1–28) reduces the output of lactose and other osmotic components from the alveoli into the gland lumen. This accounts for the coordination between the acute reductions in milk yield and milk quality in response to subclinical infection. Casein-derived peptides cause the disruption of the tight junctions between mammary epithelial cells (Shamay et al., 2002, 2003; Silanikove et al., 2013a). Casein-derived peptides are chemotactic substances that induce flow of leukocytes, mainly neutrophils, into the mammary gland lumen and explain the increase in SCC (Leitner et al., 2012). The inflammation is associated with a surge of nitric oxide that causes nitrosative stress to milk organic components and contributes further to the deterioration of milk quality (Silanikove et al., 2014b; Fig. 4.1). Plasmin-derived peptides also alter milk coagulation properties (Fleminger et al., 2011, 2013; Merin et al., 2008). The evolutionary physiological basis that underlines the reduction in milk-clotting parameters under mastitic conditions is most likely associated with the prevention of formation of coagulates that may obstruct the evacuation of secretions from the mammary glands, and thus, in turn, lead to complications, such as necrosis and uncontrolled inflammation (Leitner et al., 2011a, 2011b).

5.2 Effect of Late Lactation

Variations in milk yield and composition in goats are also affected by within and between breed variations, parity, estrous, environmental effects, and management practices (McDougall and Voermans, 2002; Leitner et al., 2007; Silanikove, 2000b; Stuhr and Aulrich, 2010; Barrón-Bravo et al., 2013). However, secondary to the important effect of IMI on milk quality is the effect of the end of lactation (Leitner et al., 2011a). In sheep, goats, and cows, end of lactation modifies the casein micelles structure and the milk-salt equilibrium, consequently altering the milk technological and physicochemical properties and cheese quality (Fedaku et al., 2005; Leitner et al., 2011a,b; Lucey and Fox, 1993). The simultaneous reduction in milk yield and milk quality is notably greater in goats than in cows and sheep (Leitner et al., 2011a). A unique feature of the end-of-lactation effect in goats is the marked elevation of SCC in milk coming from glands free of bacteria toward the end of lactation, which is associated with elevation of additional markers of inflammation (Leitner et al., 2012; Persson et al., 2014; Rota et al., 1993; Silanikove et al., 2014a; Wilson et al., 1995). The SCC in cow milk is the most important criterion used to grade milk according to its hygienic properties in Western countries. However, in dairy goats the use of this criterion is confounding due to the increase in SCC toward the end of lactation, irrespective of bacterial infection. Thus a solution to this problem is necessary before applying schemes based on SCC for goat milk. One possible solution is to use milk with the high SCC of late-lactating goats only for drinking, using bacterial isolation as the major hygienic quality criteria (Silanikove et al., 2010). Applying this solution would be simple in flocks, in which the goats are dried-off at about the same period. In multi-seasonal breeding programs, applying this solution is much more difficult, as it would require separate storage of the milk from late-lactating goats. The difficulty in applying the above-mentioned solution should be considered against the recent finding that the milk from late-lactating goats is practically worthless for cheese making (Leitner et al., 2011a).

Consistent with the model presented in Fig. 4.1, end of lactation in goats is characterized by a particular sharp increase in plasmin activity (Fantuz et al., 2001; Leitner et al., 2004a,c; 2011a) and consequently with accelerated casein breakdown. As discussed above, casein hydrolysates simultaneously reduce milk yield and impair milk clotting. Thus the larger increase in casein degradation in late lactation in goats compared to sheep and cows is explained by the more rigorous immune response and consequently more intense activation of the plasmin system (Leitner et al., 2012; Fig. 4.1).

The inflammatory response at the end of lactation may be interpreted as a pre-adaptive response to the forthcoming involution stage (Leitner et al., 2011a, 2012; Silanikove et al., 2013b). The inflammatory response in late lactation exhibits a balanced response between the leukocytes composing SCC and includes elements of the acquired immune system (Leitner et al., 2012; Silanikove et al., 2013b). Thus low milk secretion associated with balanced activation of the innate and acquired immune system allows the involution to proceed more rapidly and effectively upon induction of drying-off, to fight more effectively against existing and new infection, and to clear more effectively apoptotic cells. Goats have an advantage over sheep and cows in eradicating existing bacterial infection and resisting acquiring new infection during the dry period, which is consistent with the relatively lower levels of goats, which remained infected in the beginning of the new lactation (Leitner et al., 2007).

6. CONCLUDING REMARKS

Milk of a given mammalian species and its composition is a unique feature that provides the dairy industry with an exceptional opportunity to exploit its characteristics for human benefits, such as producing dairy products from buffalo milk, use of camel milk as a source for producing medicinal food, and use of donkey milk for producing milk with hypo-allergic qualities for infant nutrition. Qualitatively, the same factors that affect milk composition are common to all species. However, because the immune system is species-specific there is a need to increase the knowledge on factors affecting milk quality in non-cow species.

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