Compositional and functional characteristics of goat milk and relevance as a base for infant formula

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Abstract: Goat milk has a long history of use for human nutrition. There are a number of studies investigating the technofunctional properties and nutritional value of goat milk for production of consumer products such as cheese, yoghurts, and Ultra-high temperature (UHT) milks. Although fresh goat milk was traditionally used for feeding young children, use of goat milk for commercial production of formula for infants or young children has only been considered in the scientific literature since 2000s. In this review, the nutritional science relating to goat milk is discussed from the perspective of infant nutrition. A critical analysis of the scientific data concerning the composition and functional characteristics of goat milk that pertain to infant nutrition is included. From this overview, three key conclusions are possible: (1) there is a range of compositional data to support the application of goat milk for infants, provided it is fortified; (2) goat milk has the potential to influence the gastrointestinal environment differently to cow milk; and (3) the nutritional adequacy of fortified goat milk formula for newborn infants has been confirmed in clinical trials.

1. INTRODUCTION

Goats have been used as a source of milk and meat for many thousands of years (Boyazoglu, Hatziminaoglou, & Morand-Fehr, 2005). Goats have many features that benefit small communities, such as low production costs, short generation intervals, low feed requirements, and production of a constant supply of small quantities of milk suitable for immediate household consumption (Haenlein, 2004; Miller & Lu, 2019).

The global production of goat milk is growing, with most goat milk being used fresh or in processed products such as cheese or yoghurt (Miller & Lu, 2019; Sepe & Argüello, 2019). In the past, goat milk without modification was used for feeding infants (Fildes, 1986). However, the practice of feeding unmodified milk to infants less than 12 months is strongly discouraged as it brings the risk of electrolyte imbalance or deficiencies in iron, folate, or vitamin B12 (Basnet, Schneider, Gazi, Mander, & Doctor, 2010; Baur & Allen, 2005; Maines et al., 2017; Ziegler et al., 2005). Feeding unpasteurized milk carries additional risks of infections (Basnet et al., 2010).

WHO recommends exclusive breastfeeding of infants for the first 6 months, with continued breastfeeding combined with complementary foods up to the age of 2 years or beyond. Whenever breastfeeding of infants is not possible, commercial breast milk substitutes that have been appropriately manufactured and confirmed by clinical evaluation to be adequate for infant feeding may be used as alternatives (Hernell, 2012; Turck, 2013). The first commercially available formula based on goat milk was developed in the late 1980s. Initially there were concerns regarding the suitability of protein from goat milk for infants largely because the publicly available scientific evidence for the nutritional adequacy of goat milk formula was considered insufficient (EFSA, 2004).

Since that time, there have been many studies of the composition and functional characteristics of goat milk and clinical trial data concerning the use of goat milk formula as a source of nutrition for infants and young children. When this new evidence was reviewed by European Food Safety Authority in 2012, it was concluded that goat milk was suitable as a source of protein for infant and follow-on formula (EFSA, 2012). The purpose of this review is to evaluate the scientific literature concerning the use of goat milk for manufacture of infant formula. As cow milk is the most common source of protein used for making infant formula, we will highlight key features that differentiate the milk of goats and cows and hence the formula.

2. COMPOSITION OF GOAT MILK

The comparative macronutrient features of goat and cow milk have been reviewed previously (Ceballos et al., 2009; Clark & Mora Garcia, 2017; Jenness, 1980; Stergiadis, Nørskov, Purup, Givens, & Lee, 2019) and hence will not be dealt with extensively here. The key nutrients that are different between the two milks important in the context of infant nutrition are summarized in Table 1 and discussed in more detail in the following sections. The equivalent composition of human milk is included to understand the modifications necessary to produce a breast milk substitute from goat milk.

2.1 Proteins

Goat and cow milks both contain 30 to 35 g/L total protein, consisting of 80% casein and 20% whey (Ceballos et al., 2009). In contrast, mature human milk has an average of 9 g/L total protein, with approximately 40% casein and 60% whey (de Witt, 1998; Liao et al., 2017). Feeding undiluted cow or goat milk to infants is not recommended as the high protein and mineral content of both milks can result in excess amino acid intake (Raiha et al., 2002), risk of metabolic acidosis (Svenningsen, Lindquist, 1973; Turck, 2013), acute stroke (Basnet et al., 2010), and dehydration (Ziegler, 2007).

Concentrations of individual proteins varies between species (Table 2). Although human milk has no β-lactoglobulin (de Witt, 1998; Liao et al., 2017), it makes up approximately 16% of total protein of goat and cow milk. In human milk, approximately 80% of total caseins is β- and κ-casein, with only very low levels of α-casein.

Concentrations of αs1-casein in goat milk are highly dependent on the genetic polymorphisms, contributing up to 25% of total protein in milk of goats with A, B, or C alleles, whereas goats with

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Table 1–Average composition of goat, cow and human milk from published literature.

Component	Goat	Cow	Human	Reference
Total protein (g/100 mL)	3.3	3.4	0.9	Liao et al., 2017; Prosser et al., 2008
Casein (% of total protein)	83	83	27	Ceballos et al., 2009; Liao et al., 2017
Whey (% of total protein)	17	17	73	Ceballos et al., 2009; Liao et al., 2017
Lactose (g/100 mL)	4.1	4.5	6.5	Ceballos et al., 2009; Gidrewicz & Fenton, 2014
Oligosaccharides (g/L)	0.3	0.06	12	Giorgio et al., 2018
Total fat (g/100 mL)	3.5	3	3.4	Ceballos et al., 2009; Gidrewicz & Fenton, 2014
Saturated fatty acids (% of total fatty acids)	66.9	62.8	28.9	Wang, Li, et al., 2020
Medium chain fatty acids (% of total fatty acids)	18.6	12.8	4.7	Wang, Li, et al., 2020
Monounsaturated fatty acids (% of total fatty acids)	23.6	25.2	20.6	Wang, Li, et al., 2020
Polyunsaturated fatty acids (% of total fatty acids)	9.4	12	50.5	Wang, Li, et al., 2020
Calcium (mg/100 mL)	121	87	26	Ceballos et al., 2009; Gidrewicz & Fenton, 2014
Phosphorus (mg/100 mL)	104	76	16	Ceballos et al., 2009; Gidrewicz & Fenton, 2014

Table 2–Protein composition of cow, goat, and human milk.

	Goat	Cow	Human
αs2-Casein	16	8	ND
αs1-Casein	ND	27	4
β-Casein	51	34	30
κ-Casein	8	9	8
β-LG	17	16	ND
α-LA	6	4	25
Serum albumin	1	1	5
Others[a]	1	1	27

Note. Data are percent of total protein and are from Ye et al. (2019) for goat and cow milk and from Lönnerdal et al. (2016) and Liao et al. (2017) for human milk.
[a]These include lactoferrin, secretory IgA, and lysozyme that are present at 16%, 8%, and 3% of total protein in human milk, respectively.
Abbreviation: ND, not detected.

Table 3–Amino acids (mg/g N) in goat (Rutherfurd et al., 2008), cow (EFSA NDA Panel, 2004), and human milk (Zhang, Adelman, Rai, Boettcher, & Lönnerdal, 2013).

	Goat	Cow	Human
Histidine	186	168	139
Isoleucine	317	318	288
Leucine	610	625	551
Lysine	520	531	363
Phenylalanine	330	312	205
Threonine	335	300	248
Tryptophan	104	93	106
Tyrosine	265	318	264
Valine	480	394	305
Cysteine	61	50	126
Methionine	165	168	87

O or N alleles have no αs1-casein (Clark & Mora Garcia, 2017; Martin, Szymanowska, Zwierzchowski, & Leroux, 2002; Selvaggi, Laudadio, Dario, & Tufarelli, 2014). In contrast, αs1-casein in cow milk tends to be more consistent at an average 25% of total protein (Ceballos et al., 2009; Martin et al., 2002).

Lower levels of αs1-casein in goat milk give rise to larger casein micelles, with more hydrated pores than the casein micelles of cow milk (Ingham, Smialowska, Kirby, Wang, & Carr, 2018; Nguyen, Afsar, & Day, 2018; Park, Juárez, Ramos, & Haenlein, 2007; Pierre, Michel, Le Garet, & Zahoute, 1998; Remeuf, Lenoir, & Duby, 1989; Wang et al., 2019). As a consequence, goat yoghurt (Miocinovic et al., 2016; Nguyen et al., 2018) and cheese (Mestawet et al., 2014; Park et al., 2007; Pierre et al., 1998; Remeuf et al., 1989) have a less dense gel structure than their counterparts made with cow milk. The formation and secretion of casein micelles is also disrupted when αs1-casein is low or absent in goat milk (Chanat, Martin, & Ollivier-Bousquet, 1999; Neveu, Riaublanc, Miranda, Chich, & Martin, 2002).

2.2 Amino acids

The amino acid sequence of cow and goat milk proteins shares an overall 88% homology (Tsabouri, Douros, & Priftis, 2014), but only 60% homology to human milk proteins (Roncada et al., 2012). When expressed as proportion of total protein, concentrations of most amino acids in goat and cow milk are relatively similar (Table 3). Although Davis et al. (1994) indicated little difference between cow and goat milk for methionine and cysteine, more recent studies confirm more cysteine and a lower methionine to cysteine ratio in goat than cow milk (Ceballos et al., 2009; EFSA, 2004; Rutherfurd, Moughan, Lowry, & Prosser, 2008). Compared to human milk, goat and cow milk have more methionine and less cysteine and cow milk has less tryptophan (Table 3). Hence, both milks require adjustment of the individual amino acids for infant formula (EFSA NDA Panel, 2012; Turk, 2013). Feeding infants goat milk without modification of the individual amino acids may also result in excessive methionine and phenylalanine levels in infants and hence false positives in some newborn screening for inherited metabolic disorders (Chapman, Ganesh, & Ficicioglu, 2008; Maines et al., 2017).

2.3 Nonprotein nitrogen

The nitrogen in milk is derived from protein and small-molecular-weight components within the nonprotein nitrogen (NPN) fraction. In goat milk, the NPN fraction accounts for 8% of the total nitrogen compared to less than 7% in cow milk (Prosser, McLaren, Frost, Agnew, & Lowry, 2008). Human milk has 18% to 30% NPN, consisting mostly of urea, free amino acids, nucleotides, creatinine, and sialic acid (Table 4). Similarly, urea and free amino acids represent the main components of NPN in goat milk (Prosser et al., 2008). The main differences in NPN fraction of goat and cow milk are a greater concentration and more complex array of nucleotides in goat compared to cow milk (Prosser et al., 2008). As a result, a lower addition rate of nucleotides monophosphates is needed for formula made from goat milk to achieve levels comparable to human milk (Gill, Indyk, & Manley-Harris, 2012; Prosser et al., 2008).

2.4 Carbohydrate

Lactose is the preferred carbohydrate in formulas for infants (EFSA, 2014). On average, lactose is approximately 10% lower in

Table 4–Composition of nonprotein nitrogen in goat, cow, and human milk.

Component (mg/100 mL)	Goat	Cow	Human
Nonprotein nitrogen	42	38	32
Free amino acids	21	6	3.4
Taurine	9.8	0.5	3
Nucleotides	10	ND	4.2
Urea	28	22	18
Creatinine	1.4	1.8	1.1
Sialic acid	10	20	27

Note. Data for goat and cow milk are from Prosser et al. (2008) and for human milk from Carlson (1985) and Donovan and Lönnerdal, (1989).
Abbreviation: ND, not detected.

goat milk compared to cow milk, but concentrations vary (Ceballos et al., 2009; Clark & Mora Garcia, 2017). Human milk has much higher levels of lactose (Gidrewicz & Fenton, 2014).

Goat milk also contains 2′-fucosylactose, 3′- and 6′-galactosyllactose, 3′- and 6′-sialyllactose, and lacto-N-neo-tetraose (Dong, Zhou, & Mechref, 2016; Giorgio, Di Trana, & Claps, 2018; Kiskini & Difilippo, 2013; Leong et al., 2019; Martinez-Ferez et al., 2006; Meyrand et al., 2013; Wang, Zhou et al., 2020). Goats that produce no αs1-casein have similar total level of oligosaccharides, but slightly more fucosylated oligosaccharides in their milk than goats of the high-αs1-casein-producing genotype (Meyrand et al., 2013). *In vitro* studies have shown that 3′- and/or 6′-sialyllactose oligosaccharides from goat milk are preferentially catabolized by *Bifidobacteria* isolated from infants (Quinn et al., 2018; Thum, Roy, McNabb, Otter, & Cookson, 2015).

Although concentrations of oligosaccharides in goat milk are up to 10 times higher than cow milk, the natural levels in goat milk would require supplementation to attain comparable levels to human milk (Giorgio et al., 2018; Meyrand et al., 2013). New innovations in large scale production of oligosaccharides that mimic the types present in human milk have enabled their addition to formula (Vandenplas et al., 2018). However, it is not clear what outcomes would be observed if these oligosaccharides were added to formula with goat milk and whether they would work in synergy with the oligosaccharides naturally present in goat milk.

2.5 Fatty acids

Total fat content and the proportion of fatty acids are relatively similar in goat and cow milk (Ceballos et al., 2009; Prosser, Svetashev, Vyssotski, & Lowry, 2010; Yao et al., 2016) except for more medium chain fatty acids (caprylic and capric) and branched-chain fatty acids, such as 4-methyl- and 4-ethyl-octanoic acid, in goat milk fat (Ha & Lindsay, 1993; Ceballos et al., 2009; Prosser et al., 2010). These fatty acids give goat milk its characteristic flavor (Chilliard, Ferlay, Rouel, & Lamberet, 2003). Infants absorb medium-chain saturated fatty acids more readily than longer chain saturated fatty acids (Lindquist & Hernell, 2010), meaning goat milk fat may be advantageous in formula.

Analysis of the milk fat globule membrane surrounding the milk droplets of goat, cow, and human milk revealed a similar abundance of the main membrane proteins (Lu et al., 2016; Sun, Wang, Sun, & Guo, 2019). However, the minor proteins, particularly those involved with immune defense, varied considerably in abundance.

The fatty acid profile of goat milk is heavily influenced by diet as outlined in the reviews of Chilliard et al. (2003, 2014) and by the αs1-casein genotype (Chilliard, Rouel, & Leroux, 2006). Human milk has more oleic, docosahexaenoic, arachidonic acid, linoleic acid, and α-linoleic acid than goat milk (Wang, Li, et al., 2020; Yao et al., 2016). Hence, supplementation of the fatty acids of goat milk is necessary when making formula for infants.

2.6 Minerals and vitamins

As with cow milk, goat milk is an excellent source of calcium and phosphorus, but at levels that are excessive for newborn infants (Turck, 2013). In contrast, vitamin C, vitamin B12, folate, and vitamin D are inadequate for infants (Turck, 2013). Thus, the mineral and vitamin levels of both goat and cow milk must be modified for formula for infants. Riboflavin, vitamin B12, folate, and pantothenate are generally at lower concentrations in goat milk than cow milk (Ceballos et al., 2009; Park et al., 2007). Folic acid and vitamin B12 deficiencies in goat milk are a particular concern due to development of megaloblastic anemia if infants are exclusively fed goat milk that is not fortified with these ingredients (Basnet et al., 2010; Ziegler et al., 2005).

3. FUNCTIONAL PROPERTIES OF GOAT MILK

3.1 Digestion

The digestive properties of proteins are important when considering the source of the proteins for infant formula as the digestive capacity of the infant stomach is lower than adults (Bourlieu et al., 2014). The more open structure with thinner protein strands of the acid-induced coagulate from goat milk (Wang et al., 2019; Ye, Cui, Carpenter, Prosser, & Singh, 2019) is a potential advantage for goat milk over cow milk as this would allow greater diffusion of pepsin and hence digestion of the casein proteins (Thévenot, Cauty, Legland, Dupont, & Floury, 2017). In keeping with this, casein proteins from goat milk are digested more effectively than caseins from cow milk under adult (Almaas et al., 2006; Tagliazucchi, Martini, Shamsia, Helal, & Conte, 2018) and infant (Hodgkinson, Wallace, Boggs, Broadhurst, & Prosser, 2018; Ye et al., 2019) gastric conditions *in vitro*. In a study with rodents, consumption of goat milk also induced faster stomach emptying compared to cow milk, most likely linked to the different coagulation properties of the two milks (Dalziel et al. (2020)).

Gastric digestion of cow or goat milk also produced peptides unique to each species (Hodgkinson, Wallace, Smolenski, & Prosser, 2019). The majority of the identified peptides were from β-casein, with low numbers of peptides from β-lactoglobulin, consistent with the latter protein being resistant to pepsin digestion (Hodgkinson et al., 2018; Ye et al., 2019). Similarly, β-casein produced most of the unique peptide sequences after gastric digestion of human milk *in vivo* (Dallas et al., 2014) or *in vitro* (Wada & Lönnerdal, 2015a). Thirty-eight individual peptides were identified from goat milk with antimicrobial, ACE-inhibitory, antioxidant, immunomodulatory, opioid, or dipeptidyl peptidase-IV inhibitory bioactivity, but only 10 of them were similar to cow milk (Hodgkinson et al., 2019). Of these, two peptides from β-casein of cow milk had a similar sequence to peptides from β-casein of human milk (Wada & Lönnerdal, 2015a). The clinical relevance of peptides produced during digestion of milk of any species is not known.

Although there is differential gastric digestion of proteins from cow and goat milk, the intestinal absorption of amino acids from goat or cow milk in adults was very similar (Milan et al., 2018). Similarly, the ileal digestion of amino acids from goat or cow milk proteins was comparable in piglets (Rutherfurd, Darragh, Hendriks, Prosser, & Lowry, 2006a) or when assessed *in vitro* (Maathuis, Havenaar, He, & Bellmann, 2017). These findings indicate that any differences in gastric processing of goat milk and hence early digestion outcomes are unlikely to impact intestinal digestion or bioavailability of amino acids from goat milk proteins.

In comparative studies with cow milk, the digestive utilization of goat milk fat was greater than that of cow milk fat in a rodent model of fat malabsorption (Alferez et al., 2001), in children with gluten intolerance (Hachelaf et al., 1993) and in undernourished children (Razafindrakoto et al., 1993). The authors of these studies attributed the greater utilization of goat milk fat to the medium-chain saturated fatty acids in goat milk. Although the smaller size of fat droplets in goat milk compared to cow milk has also been suggested to contribute to differences in digestion of milk fat (Attaie & Richter, 2000), there is no evidence for this. In addition, it is unlikely to be a factor in processed milks or milk products, where homogenization creates a more uniform fat droplet size (Attaie & Richter, 2000).

3.2 Gastrointestinal function and gut microbiome

There are several reports associating goat milk with reduced symptoms of abdominal pain, bloating, or diarrhea (Haenlein, 2004; Jerop, Kosgey, Ogola, & Opondo, 2014; Park, 1994; Santosa, Setiadi, Kisworo, & Nuswantara, 2012). It is possible that the weaker structure of the acid-induced coagulate of goat milk (Wang et al., 2019) and faster emptying of solids from the stomach (Dalziel et al., 2020) might translate to differences in perceptions of abdominal pain, but this is yet to be confirmed.

Studies in rodents suggest that goat milk may partially protect against damage to the intestine due to heat stress (Prosser et al., 2004) or intestinal inflammation (de Assis et al., 2016). Changes in the fermentation indices of short-chain fatty acids in rodents-fed goat milk (Paturi et al., 2018) and amelioration of inflammatory reactions in rodent models of colitis by goat-derived oligosaccharides (Daddaoua et al., 2006; Lara-Villoslada et al., 2006) are consistent with goat milk having the potential to lower intestinal inflammation. Goat milk had a greater effect on the intestinal microbial community and on metabolism of mice than cow milk (Wang et al., 2018). Goat milk also prevented the adhesion of *Escherichia coli* and a *Salmonella typhimurium* isolate to Caco-2 cells (Leong et al., 2019). Additionally, oligosaccharides from goat milk enhanced the adhesion of *Bifidobacteria longum* subsp. *infantis* to HT-29 intestinal cells by eightfold compared to oligosaccharides of cow milk (Quinn et al., 2018). The above studies suggest goat milk may influence the gastrointestinal environment and metabolism differently to cow milk and further research in this area, particularly clinical trials with human subjects, is warranted.

3.3 Mineral absorption

When mineral uptake was assessed in rodent models of compromised intestinal absorption capacity, goat milk was found to enhance utilization of calcium, phosphorus, iron, copper, zinc, magnesium, and selenium more than cow milk (Barrionuevo, Alferez, Lopez-Aliaga, Sanz-Sampelayo, & Campos, 2002; Campos, Lopez-Aliaga, Alferez, Nestares, & Barrionuevo, 2003; López-Aliaga et al., 2003). In rodents with iron anemia, goat milk enhanced efficiency of hemoglobin regeneration more than cow milk (Park, Mahoney, & Hendricks, 1986), improved bioavailability of iron and magnesium (Nestares et al., 2008), and also improved bone health (Diaz-Castro et al., 2011).

Conversely, in vitamin D-deficient rats, there was no difference in vitamin D or calcium absorption when fed either goat or cow milk fortified with vitamin D (Hodgkinson, Wallace, Kruger, & Prosser, 2018; Mora-Gutierrez, Farrell, Attaie, McWhinney, & Wang, 2007). Nor were there any differences in mineral bioavailability from fortified goat or cow milk in a 3-week-old piglet model of infant digestion (Rutherfurd, Darragh, Hendriks, Prosser, & Lowry, 2006b). Thus, the relative efficacy of mineral adsorption of fortified goat compared to fortified cow milk may depend on the physiological status of the recipient. Conversely, these studies confirm that goat milk would be just as effective as cow milk as a source of minerals or vitamins when these are fortified in formula for infants.

Table 5–Incidence of allergy related reactions in children attributed to cow or goat milk.

Goat	Cow	*n*	Reference
4%	22%	54	Novembre et al., 1998
0.3%	8.3%	544	Rancé, Kanny, Dutau, & Moneret-Vautrin, 1999
<0.7%	28.4%	740	Lee, 2017

3.4 Food intake

In a study investigating satiating effects of goat milk in adults, Rubio-Martín et al. (2017) found the desire-to-eat rating was significantly lower and hunger rating tended to be lower after a breakfast with goat milk, suggesting a slightly higher satiating effect compared to cow milk. However, Milan et al. (2018) showed no differences in scores for hunger, fullness, and desire to eat sweet, salty, savory, or fatty food when fortified goat or cow milk was given after an overnight fast. When offered concurrently to rodents, goat milk was preferred over cow milk, irrespective of age of the animals (Klochars et al., 2019). Gene expression within the feeding-relevant brain circuit confirmed this preference for goat milk was driven by central mechanisms controlling eating for pleasure. Whether this finding relates to feeding behavior in adults or infants has not been established.

3.5 Allergy

Both cow and goat milks contain potentially allergic proteins, but allergy to goat milk was less frequently reported than allergy to cow milk in at least three publications (Table 5).

Goat milk was also less allergenic than cow milk when introduced into the diet of rats at weaning (Lara-Villoslada, Olivares, Jiménez, Boza, & Xaus, 2004). However, there are also reports of reactions to goat milk cheese in children where there was no other evidence of allergy to cow milk (Ah-Leung et al., 2006; Bidat, Rancé, Baranès, & Goulamhoussen, 2003; Raghani et al., 2016). The average age of first allergic response to goat milk cheese was 5 to 6 years, which is later than when allergy to cow milk is commonly reported (Ah-Leung et al., 2006; Bidat et al., 2003; Raghani et al., 2016). This delay in response is likely to reflect the later age of exposure to goat milk proteins.

Some children already sensitized to cow milk may also react to goat milk proteins (Bellioni-Businco et al., 1999; Restani et al., 1999; Spuergin et al., 1997). For example, in two oral challenge studies, 75 and 90% of children with allergy to cow milk proteins also reacted to goat milk (Bellioni-Businco et al., 1999; Infante, Tormo, & Conde, 2003). Nevertheless, five times more goat milk was required to trigger an adverse reaction indicating the milks elicited a different allergic response (Bellioni-Businco et al., 1999). Bevilacqua et al. (2001) suggested that allergy to goat milk may differ to cow milk due to the lower concentrations of αs1-casein of goat milk. In keeping with this, the severity of the immune response in rodents presensitized to αs1-casein was reduced when challenged with a low dose of αs1-casein (Hodgkinson et al., 2012). Children with allergy to cow milk proteins also had a lower antibody response when exposed to goat milk containing low amounts of αs1-casein (Ballabio et al., 2011). Lymphocytes from children with allergy to cow milk produced less of the pro-inflammatory cytokine TNF-α and more of the anti-inflammatory cytokine IL-10 when stimulated with goat milk or a goat casein fraction with less αs1-casein than cow milk (Albenzio et al., 2012). Lisson, Novak, and Erhardt (2014) further demonstrated a significant difference in binding of αs1-casein variants from goats to IgE, where epitopes differed by two amino acids and in some cases only one amino acid. The study by Bevilacqua et al. (2001) was different from each of these studies, however, as the animal model was based on sensitization to β-lactoglobulin, not αs1-casein. The authors suggested that the effect of goat milk was not just related to an immune reaction to αs1-casein, but perhaps indirectly to differences in protein digestion.

From the above studies, it is clear that goat milk is not hypoallergenic as some have proposed (Haenlein, 2004; Park, 1994). Therefore, infant formula based on goat milk proteins is not recommended for use in treatment of children with acute symptoms of cow milk protein allergy and it is important to investigate possible cross-reactivity to goat milk if already sensitized to cow milk. Further experiments are also needed to confirm the potential mechanisms underlying any differential immunogenic reactions to goat and cow milk.

4. STUDIES OF INFANT FORMULA

4.1 Composition

The nutritional requirements for infant formula are largely based on the composition of human milk (EFSA, 2014; Koletzko et al., 2005). The proteins of cow and goat milk require dilution to reduce renal solute load and addition of lactose and specific vitamins and minerals to meet nutritional requirements of infants. The addition of lactose acts to lower the protein to energy ratio of the milks, whereas deficiencies in folic acid or vitamin B12 are overcome by fortification (de Witt, 1998; Turck, 2013).

Formula based on cow milk proteins typically has whey proteins added to mimic the 60:40 whey to casein ratio of human milk (de Witt, 1998; Heird, 2007). Such formula is frequently referred to as "whey-enhanced." Whey from human milk contains lactoferrin, α-lactalbumin, and immunoglobulins, but no β-lactoglobulin (de Whit, 1998; Liao et al., 2017; Lönnerdal, Erdmann, Thakkar, Sauser, & Destaillats, 2016), whereas whey from cow or goat milk contains significant amounts of β-lactoglobulin, but lower α-lactalbumin and very little lactoferrin and immunoglobulins (de Whit, 1998; Roncada et al., 2012; Ye et al., 2019). Whey-enhanced formula can have up to three times more β-lactoglobulin, unless concentrations of this protein are reduced by processing (de Whit, 1998; Lien, 2003). Whey-enhanced formula is more susceptible to heat-induced glycation of milk proteins during processing (Meyer, Al-Diab, Vollmer, & Pischetsrieder, 2011; Prosser, Carpenter, & Hodgkinson, 2019) that may reduce their digestibility (Wada & Lönnerdal, 2015b) and perturb the growth of specific gut bacteria (Sequir, Rubio, Peinado, Delgado-Andrade, & Navarro, 2014).

Whey is also used to adjust amino acid balance of cow milk formula, particularly at low protein to energy ratios (Raiha et al., 2002). Whey-enhanced formula from goat or cow milk has similar protein quality (Maathuis et al., 2017). However, the earlier study by Rutherfurd et al. (2008) confirmed that a formula made from whole goat milk without adding whey can also satisfy the protein and amino acid requirements for formulas. Avoiding whey addition minimized levels of β-lactoglobulin (Ye et al., 2019) and protein glycation (Prosser et al., 2019). The casein curd from goat milk without added whey also had a similar curd strength as cow milk formula with a 60:40 whey to casein ratio (Wang et al., 2019).

The use of whole goat milk as the only source of proteins in formulas allows alternative sources of fat to be considered. Formulas must contain 500 to 1,200 mg/100 kcal of linoleic acid, 50 to 100 mg/100 kcal of α-linolenic acid, and less than 3% trans-fatty acids (EFSA, 2014). It is also recommended that docosahexaenoic acid up to 0.5% of the fat and at least an equal amount of arachidonic acid are present (Koletzko, Carlson, & van Goudoever, 2015). The low levels of oleic, linoleic acid, and α-linolenic acid and only trace amounts of docosahexaenoic or arachidonic acid in milk fat mean that formulas must have an additional source of these fatty acids, predominantly from vegetable oils (Delplanque, Gibson, Koletzko, Lapillonne, & Strandvik, 2015; Wei, Jin, & Wang, 2019). Although a formula made with goat milk can use vegetable oils only (Maduko & Park, 2007), it is also possible to use a mixture of goat milk fat and vegetable oils to meet the required fatty acid profiles when formula is made from whole goat milk (Gallier, Tolenaars, & Prosser, 2020; Prosser et al., 2010). Including milk fat reduces exposure of the infant to phytosterols (Claumarchirant, Matencio, Sanchez-Siles, Alegría, & Lagarda, 2015), while retaining milk fat globule membrane components that are lacking in vegetable oils (Gallier et al., 2020; Hageman, Danielsen, Nieuwenhuizen, Feitsma, & Dalsgaard, 2019; Heird, 2007).

Thus, formulas may be either whey enhanced with a 60:40 whey to casein ratio or retain original 20:80 whey to casein ratio of goat milk. Formulas may also contain a mixture of vegetable oils with goat milk fat or vegetable oils only. To date, a direct comparison of the performance of goat formulas with different proportions of whey proteins or source of fat has not been conducted. However, animal studies indicate that there would be minimal differences in performance of goat milk formulas with different amounts of whey. In weanling rats, calcium absorption was 34% greater with diets containing 80% casein from goat milk compared to 17% casein (McKinnon, Kruger, Prosser, & Lowry, 2010). Piglet studies confirmed that the bioavailability of minerals and amino acids from formulas made with goat milk without added whey was comparable to whey-enhanced formulas made with cow milk (Rutherfurd et al., 2006a, 2006b). It is possible that goat milk fatty acids might contribute to better absorption of minerals, because goat milk fortified with minerals and vitamins was more effective at improving calcium and phosphorus absorption and retention in growing rats when it contained goat milk fat compared to vegetable oils (Kruger et al., 2008).

4.2 Clinical evaluation

To date, there has been one prospective cohort study and three double blinded, randomized, control trials that have assessed the growth of newborn infants fed formula based on the proteins of goat milk and compared to formula with proteins from cow milk. The prospective cohort study followed a total of 976 infants who were fed breast milk, goat milk formula without added whey, whey-enhanced cow infant formula, or a combination of formula and breast milk for first 4 months of life (Han et al., 2011). Infants fed breast milk, either of the formula types, or a combination of breast milk and formula displayed similar growth outcomes out to 12 months (Han et al., 2011).

The first double blinded, randomized, control trial of goat milk formula involved 62 infants, from birth to 6 months of age (Grant et al., 2005). A second 12-month study had 200 infants randomized to either cow or goat formula and a parallel group of 100 breast-fed infants (Zhou, Hawke, Collins, Gibson, & Makrides, 2020). Both trials employed a goat milk infant formula with 20:80 whey to casein ratio and a mixture of goat milk fat and vegetable oils compared to a conventional cow milk infant formula with a whey to casein ratio of 60:40 and without milk fat. Neither formulas had added prebiotics. A third trial compared goat and cow milk–based formula, both having added whey proteins and no milk fat, in 79 infants up to 6 months of age (Xu et al., 2015). In all three trials, growth of the infants fed goat milk formula did not differ from infants fed the cow formula (Grant et al., 2005; Xu et al., 2015; Zhou et al., 2014). There were small differences in growth of breastfed infants with those fed either the cow or goat formula, but these were not considered to be clinically significant (Zhou et al., 2014). Body composition of infants fed goat milk or cow milk formula were also comparable to breast-fed infants (Zhou et al., 2020).

The study by Zhou et al. (2014) was the first to also record a wide range of outcomes related to general health, gastrointestinal function, and allergy using a combination of objective clinical assessments and subjective parental reports. There were no differences between infants fed goat formula compared to cow formula or a reference population of breast-fed infants for an extensive range of health-related outcomes or the occurrence of serious adverse events, thus supporting the safety of using goat milk in infant formula for newborn infants through the first 12 months of life.

Blood levels of folate, ferritin, hemoglobin, and hematocrit of infants fed the goat formula were comparable to breast fed infants (Zhou et al., 2014) confirming adequate supply of folate and iron. There were minor differences in the plasma amino acid profile of formula fed- and breast-fed infants, whereas blood urea nitrogen was 11% lower in infants fed the goat formula compared to the whey-based cow formula (Zhou et al., 2014). Blood urea nitrogen is linked to an imbalance in amino acid supply (Raiha et al., 2002). Hence, the results suggest less risk of excess amino acids in goat formula without whey adjustment compared to cow milk formula with added whey. As no data are available on plasma amino acids or urea in blood of infants fed goat formula with added whey (Xu et al., 2015), it is not possible to determine what effect the added whey proteins from goat milk have on the amino acid uptake by infant.

There were higher concentrations of glycerophospholipids containing myristic acid and palmitoleic acid in plasma of infants fed formula with goat milk fat compared to the formula with vegetable oils only, reflecting the presence of the milk fat in the formula (Uhl et al., 2015). Other than these two fatty acids, there were no differences in the fatty acids in the glycerophospholipids in plasma, suggesting similar digestion and absorption from the fat blends in the two formulas.

When compared to the microbiota of infants fed breast milk, the microflora of infants fed goat milk were more similar than cow milk formula–fed infants (Tannock et al., 2013). Stools of all infants contained *Bifidobacteriaceae* and *Lachnospiraceae*. As neither formulas had added prebiotics, further studies in this area would help to understand the nature of the compounds that maintain *Bifidobacteriaceae* when oligosaccharides are low (Tannock et al., 2013).

According to Grant et al. (2005), infants who were fed formula with proteins and fat from goat milk had looser stools compared to infants fed cow milk proteins and vegetable oils, whereas Zhou et al. (2014) reported no significant differences between the two formula groups. In the prospective cohort study (Han et al., 2011), infants fed goat formula were more likely to have softer stools that more closely resembled those of infants fed breast milk than those infants fed cow formula. In a case series study, infants with symptoms of constipation when fed formulas based on cow milk proteins had softer stools with a lower fat content and fewer episodes of prolonged crying after changing to infant formula with proteins and fat from goat milk (Infante, Prosser, & Tormo, 2018). None of the formulas in these studies had added prebiotics.

Finally, there were no differences in the objective assessments of allergy-related outcomes including dermatitis and medically diagnosed food allergy, but there was a trend for reduced eczema in infants randomized to goat milk formula compared to cow milk formula (14% compared to 23%, respectively; Zhou et al., 2014). As the trial was powered to assess growth outcomes, not eczema, the difference was not statistically significant. A much larger randomized controlled trial is needed to determine whether there is any advantage when using goat milk formula in early life compared to cow milk formula for development of eczema.

5. CONCLUSION AND PERSPECTIVE

Although there is still much to learn about goat milk, it is clear that it offers a different choice to consumers who seek alternatives to cow milk products. Based on compositional data, formulas with ingredients sourced from whole goat milk to retain the milk fat and fortified with lactose, essential fatty acids, and vitamins, but without the addition of whey, can meet the compositional requirements for infant formula. Clinical trials further confirm the nutritional adequacy and safety of a formula made with proteins and fat from whole goat milk. Many of the compositional and functional features of goat milk that differ from cow milk may also be important when assessing the biological function of goat milk for humans. For example, there is accumulating preclinical evidence to suggest that goat milk may influence the gastrointestinal environment and allergy-related immune pathways differently to cow milk. These findings have direct application for infants because of the relative immaturity of the infant gut and immune system. However, there is a need for more translational research and clinical trials to confirm the positive differences in gastrointestinal and eczema-related outcomes for infants as to date most evidence is from *in vitro* or animal studies only. Clinical trials to explore the gut microbiota of infants fed goat compared to cow formula and to determine whether supplementation of the natural milk oligosaccharides within goat milk formula could also benefit the microbiota diversity of infants are also warranted.

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AUTHOR CONTRIBUTIONS

C. Prosser was responsible for the conception, planning, interpretation, and writing of the manuscript.

CONFLICTS OF INTEREST

The author is an employee of Dairy Goat Co-operative (N.Z.) Limited that develops, manufactures, and researches goat milk infant formula.

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