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Invited review: Human, cow, and donkey milk comparison: Focus on metabolic effects

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ABSTRACT

Milk is an important food of the daily diet. Many countries include it in their dietary recommendations due to its content in several important nutrients that exert beneficial effects on human health. Human milk is a newborn's first food and plays an important role in the growth, development, and future health of every individual. Cow milk is the type of milk most consumed in the world. However, its relatively high content of saturated fats raises concerns about potential adverse effects on human health, although epidemiological studies have disproved this association. Indeed, dairy consumption appear to be linked to a lower risk of mortality and major cardiovascular disease events. In the last few years many researchers have begun to focus their attention on both the production and quality of cow milk as well as the analysis of milk from other animal species to evaluate their effect on human health. The need to investigate the composition and metabolic effects of milk from other animal species arises from the adverse reactions of individuals in several groups to certain components of cow milk. It has emerged that donkey milk compared with that of other animal species, is the nearest to human milk and an excellent substitute for it. Milk from various animal species shows substantial differences in nutritional composition and distinct metabolic effects. In this review, we discussed the main compositional features and metabolic effects of 3 types of milk: human, cow, and donkey milk.
Key words: human milk, donkey milk, cow milk, metabolic effects

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INTRODUCTION

Mammalian milk is a complex biological fluid produced by mammary glands. It is the first natural food for mammals, supplying all the energy and nutrients needed for proper growth and development in the postnatal period. Milk is a potential source of various macro- and micronutrients (Gaucheron, 2011; Kim and Yi, 2020). It contains nutrients such as carbohydrates, lipids, minerals, proteins, vitamins, and other nutritional components, which help to promote nutritional and other desirable health benefits (Ebringer et al., 2008). Indeed, milk contains potential bioactive components, which aids in the maintenance of the proper metabolism and functioning of the human body. Contrary to other mammals, milk consumption by humans does not stop at the end of the weaning period but continues into adulthood. The worldwide commercial production of cow milk (**CM**) is decisively higher compared with other animal species, reaching about 83% of global consumption (Bittante et al., 2022). To date, several groups of individuals experience adverse reactions to some components of CM (Hochwallner et al., 2014). Therefore, research on alternative milks has intensified in recent decades. Suitable alternatives to milk include CM protein hydrolysates, AA formulas, soy, and rice drinks (Verduci et al., 2019a). However, some of these products still have allergenic potential and do not represent a complete food. Further, some alternative kinds of milk have an unpleasant taste and are often rejected by infants. Therefore, the identification of a natural, palatable, and hypoallergenic milk is thus of great interest. In addition, in recent years, given the growing evidence supporting the association between nutrition and health, consumer interest in the nutritional quality of milk has increased enough to encourage scientific research on the composition and health effects of different types of milk.

Table 1. Summary of studies comparing the composition and metabolic effects among different types of milk; publications were chosen based on the simultaneous study of at least 2 of the 3 types of milk examined in this review and at least one criterion between evaluation of composition or metabolic effects

		Milk comparison			Evaluated aspects	
Authors	Title	Cow milk	Donkey milk	Human milk	Composition	Metabolic effects
Lionetti et al., 2012	Diet supplementation with donkey milk upregulates liver mitochondrial uncoupling, reduces energy efficiency, and improves antioxidant and anti-inflammatory defenses in rats	√	√			√
Claeys et al., 2014	Consumption of raw or heated milk from different species: An evaluation of the nutritional and potential health benefits	√	√	√	√	
Trinchese et al., 2015	Human, donkey and cow milk differently affects energy efficiency and inflammatory state by modulating mitochondrial function and gut microbiota	√	√	√		√
Vincenzetti et al., 2017	Role of proteins and of some bioactive peptides on the nutritional quality of donkey milk and their impact on human health	√	√	√	√	
Trinchese et al., 2018	Human milk and donkey milk, compared with cow milk, reduce inflammatory mediators, and modulate glucose and lipid metabolism, acting on mitochondrial function and oleoylethanolamide levels in rat skeletal muscle	√	√	√	√	
Altomonte et al., 2019	Donkey and human milk: Insights into their compositional similarities		√	√	√	
Mollica et al., 2021	Milk fatty acid profiles in different animal species: Focus on the potential effect of selected PUFA on metabolism and brain functions	√	√	√	√	√
Trinchese et al., 2021	Heart mitochondrial metabolic flexibility and redox status are improved by donkey and human milk intake	√	√	√	√	

This review gives salient insights into the key nutritional components and bioactive constituents present in 3 widely studied types of milk (human, cow, and donkey) and provides an overview of their main metabolic implications. The main studies examined on comparison of 2 or 3 different types of milk in terms of composition and metabolic effects are reported in Table 1. In particular, in some of these papers the metabolic effects of 3 types of milk on organs with the highest metabolic rate are considered simultaneously, and for this reason were selected.

COMPOSITION OF HUMAN MILK

Human milk (**HM**) contains a variety of components that play an important role in supporting early human growth and development (Agostoni et al., 2009; Cheema et al., 2021). In recent years, the association between HM components and infant health benefits has been investigated and continues to attract intense research attention. Human milk is rich in water, contains micronutrients such as carbohydrates, protein, and fat (Martin et al., 2016). Carbohydrates play a significant role in infant nutrition, and in the development and maintenance of the gut microbiota composition (Flint, 2012). Lactose is the major HM carbohydrate constituent and is present in higher concentrations than in the milk of ruminant species, and similar to donkey milk (**DOM**) as reported in Table 2. It favors the uptake and attachment of bioactive milk components, such as oligosaccharides and minerals (Medeiros et al., 2012; Martin et al., 2016). Oligosaccharides are the second most abundant carbohydrates in HM, synthesized in the mammary gland from lactose. They do not provide direct nutritional value, but play an important prebiotic role in the development of gut microbiota and the immune system in early stages after birth (Walsh et al., 2020). Oligosaccharides from HM have been extensively studied and over 200 different oligosaccharides have been identified (Licitra et al., 2019). Fucosylated oligosaccharides make up the majority of the oligosaccharides in HM of most mothers. Fucosylated oligosaccharides play important antiadhesive properties against fucose-dependent pathogens and are crucial for growth and metabolism of beneficial bacteria, participating in shaping a healthy microbiome (Orczyk-Pawiłowicz and Lis-Kuberka, 2020). Oligosaccharides can indirectly increase short-chain fatty acid (**SCFA**) production by certain bacteria species. The SCFA are an important energy source for enterocytes and key molecules in maintaining bowel health (Plaza-Díaz et al., 2018).

The proteins in HM are divided into the whey and casein fractions that include various peptides with bioactive functions. Each fraction comprises a range of specific proteins and peptides (Liao et al., 2011). Caseins are present in α, β, gamma, and kappa isoforms. The major constituent of human caseins is β-CN, a highly phosphorylated protein (Greenberg et al., 1984) that contributes to the high bioavailability of calcium from HM, and may also affect the absorption of other divalent cations (Hansen et al., 1996). The most abundant whey proteins are IgA, lactoferrin, α-LA, and lysozyme (Lönnerdal, 2003). The IgA accounts for about 90% of the total immunoglobulins in HM; it plays an important role in pathogen binding, preventing their adherence to the intestinal mucosal surface (Lönnerdal, 2003). Lactoferrin is an iron-binding glycoprotein that plays a crucial role in preventing pathogens growth and proliferation, thus carrying out a strong bactericidal activity (Arnold et al., 1980; Wakabayashi et al., 2006). Lactoferrin is also involved in promoting the growth of probiotic bacteria (Albenzio et al., 2016).

α-Lactalbumin is a small Ca^{2+}-binding protein that plays a significant role on mineral absorption (Lönnerdal and Glazier, 1985). The crucial biological role of α-LA is to regulate activity of lactose synthase in mammary secretory cells (Permyakov, 2020). Lysozyme is present at a high concentration in HM (Chandan et al., 1968) and plays an important role in inhibiting the spread of bacterial pathogens. The whey/casein ratio changes in relation to the onset of lactation as among different animal species. The HM lipids provide a major portion of the total energy intake and essential micronutrients in the infant, such as lipid soluble vitamins, PUFA, and bioactive components (Delplanque et al., 2015). On average, HM contains 4.0% fat, of which about 95 to 98% is found in the triglyceride form (Khor et al., 2020). It is characterized by a high content of palmitic acid (C16:0), concentrated in the 2-position and oleic acid (C18: 1n-9), concentrated in the 1- and 3-positions of the triglycerides. The fatty acids most represented in HM are C10-C18; 2 essential fatty acids are also represented, namely linoleic acid (**LA**; C18:2 n-6) and linolenic acid (**ALA**; C18:3 n-3; Demmelmair and Koletzko, 2018), both not synthesized in humans. In addition, arachidonic acid (**ARA**) is a common long-chain PUFA in HM. Arachidonic acid plays an important role in physiological development and its related functions during early childhood nutrition are well known. Well-fed mothers' HM has adequate levels of ARA to support the nutritional and developmental needs of babies (Salem and Van Dael, 2020). The fatty acid profile of HM varies in relation to maternal diet, particularly, for long-chain PUFA (Aumeistere et al., 2019). There is evidence that vitamin levels in HM are affected by the maternal intake and body stores. In general, water-soluble vitamin levels appear more responsive to maternal dietary intake than levels of fat-soluble vitamins and minerals. Human milk contains adequate amounts of most vitamins to support normal infant growth, with the exception of vitamins D and K. Indeed, vitamin D and vitamin K status are possible issues for breastfed infants. Vitamin K traverses the placenta from mother to infant very poorly, and it is present only in very low concentrations in HM, resulting in low serum levels of vitamin K in infants (Greer, 1999). Vitamin D plays an important role in infant bone growth, immune system regulation and brain development, but is found in low quantities in HM. To date, it is necessary for infants to be supplemented with vitamin K and vitamin D early in lactation; iron supplements over 6 mo of age may be indicated to buffer for insufficient reserves and inadequate transfer via breastfeeding (Dror and Allen, 2018). See Table 2 for a comparison of the HM component with those of the other milks examined.

Table 2. Human, cow, and donkey milk composition

Item[1]	Human	Cow	Donkey
Water (%)	87.6	87.6	90.4
DM (g/L)	107–129	118–130	88–117
Lactose (g/L)	63–70	44–66	58–74
Protein (g/L)	9–19	30–39	14–20
Fat (g/L)	21–40	33–54	3–18
Total casein (g/L)	2.4–4.2	24.6–28.0	6.4–10.3
Total whey protein (g/L)	6.2–8.3	5.5–7.0	4.9–8.0
Casein/whey protein ratio	0.4–0.5	4.5	1.3
Major casein (g/L)			
α_{S1}-CN	0.9–1.9	3.0–3.9	1.4–2.0
β-CN	3.87	8.6–11.0	3.9
Major whey protein (g/L)			
β-LG	Absent	3.2–4.0	3.2–3.7
α-LA	1.9–3.4	1.0–1.5	1.8–3.0
Lysozyme	0.04–0.2	Trace	1.0
Fatty acid (% of total fatty acids)			
SFA	39.4–45	55.7–72.8	46.7–67.7
MUFA	33.2–45.1	22.7–30.3	15.3–35.0
PUFA	8.1–19.1	2.4–6.3	14.2–30.5
C18:2	6.0–17.7	1.2–3.0	6–15.2
C18:3	0.6–3.4	0.3–1.8	4–16.3
n-6: n-3	7.4–8.1	2.1–3.7	0.9–6.1

[1]C18:2 (linoleic acid), C18:3 (α-linolenic acid). Source adapted and modified from Claeys et al. (2014) and Vincenzetti et al. (2017).

METABOLIC EFFECTS OF HUMAN MILK

Human milk represents the primary nutrition for infants, and its intake is recommended during the first 6 mo of life and later, in addition to complementary feeding (Agostoni et al., 2009). Several data indicate that HM cannot be considered mere food, but rather, an important predictor for the newborn future health. Several studies have associated HM intake to reducing the risk of developing a variety of diseases, including noncommunicable diseases such as obesity, type 2 diabetes mellitus, and cardiovascular diseases (**CVD**) later in life (Leon and Ronalds, 2009; Verduci et al., 2019b). However, these studies are carried out under different conditions and the effects described are presumed and cannot be proven by a randomized clinical trial for ethical reason. The HM is rich in bioactive molecules such as lactoferrin, lysozyme, oligosaccharides, fatty acids, and various antioxidants shown to contribute to short- and long-term health outcomes. Several studies on HM have been carried out both in vitro and in animal models to analyze the human health benefits of different components of milk. The positive benefits of oligosaccharides in HM are well known to involve multiple pathways and affect different target organs. The oligosaccharides are involved in protection against infections, in gut microbiota maturation and in brain development (Kunz et al., 2000, 2008; Pisa et al., 2021). Studies carried out on nonobese diabetic animal model have been demonstrated the role of oligosaccharides derived from HM, against the development of type 1 diabetes by influencing the intestinal microbiota, known to directly regulate immune responses (Xiao et al., 2018).

The protective role of HM and its inverse association with the duration of lactation and the incidence of type 2 diabetes in young and middle-aged women have been demonstrated (Stuebe et al., 2005). Human milk contains bioactive substances that promote satiety and energy balance, contributing to metabolism regulation and antagonizing obesity and diabetes (Li et al., 2021). Several studies show that breastfeeding and formula-feeding may have different effects on later weight of babies. Breastfed babies are better able to self-regulate the amount of energy they consume than bottle-fed babies (Bartok and Ventura, 2009). Indeed, although milk powder is a meal of constant volume and energy content, HM is not a uniform product, modifying the energy content and other properties within a 24-h period; therefore, the infants respond to this variation, adapting their intake of milk (Dewey and Lönnerdal, 1986), for example, consuming lower volumes if the milk is higher in fat content (Tyson et al., 1992). Studies conducted on murine models demonstrated the beneficial effects exerted by HM on lipid metabolism due to the increased mitochondrial functionality in skeletal muscle, and increased levels of oleoylethanolamide (**OEA**) in the liver and skeletal muscle compared with control animals. Specifically, OEA levels in the liver are about 30 versus 18 nmol/g in HM and control animals, respectively, whereas in skeletal muscle OEA levels are about 310 and 210 nmol/ g in HM and control animals, respectively (Trinchese et al., 2018). The increase in OEA levels have an important implication in terms of energy metabolism, and it is related to the high concentration of palmitic acid in the sn-2 position of the triglycerides in HM (Contreras et al., 2013; Carta et al., 2015; Innis, 2016). Moreover, studies highlighted the correlation between low blood glucose and insulin in infancy and low insulin levels in adulthood (Owen et al., 2006). The ability of HM to control glucose homeostasis and decreased insulin resistance has been demonstrated in animal model fed with HM supplementation (Cani et al., 2007; Trinchese et al., 2015). The beneficial effects of HM on glucose homeostasis may be the result of its modulation of the gut microbiota (Cani et al., 2007). Several studies have reported that the fat percentage energy in HM is inversely associated weight gain and adiposity during infancy, suggesting that HM macronutrients have functional implications (Prentice et al., 2016). The quality and quantity of fatty acid components, such as SCFA, are relevant to infant growth. Although it is well known, the SCFA in milk are much lower than those made from milk oligosaccharides by the microbial community, some studies highlight a negative association between SCFA, such as butyrate, formic acid, and acetate detectable in HM with the amount of infant adiposity (Prentice et al., 2019). Many studies have shown consistently that butyrate is involved in regulating lipid metabolism and BW gain in animal models and is able to modulate the mechanisms of immune tolerance (Mollica et al., 2017; Paparo et al., 2021). Recent data highlight the ability of oral sodium butyrate supplementation to enhance intestinal-induced dysfunction, dysbiosis, and liver-induced injury (Pirozzi et al., 2020; Avagliano et al., 2022; Cristiano et al., 2022).

In addition, it is capable to enhance the intestinal barrier by regulating the assembly of tight junctions, strengthening the epithelial barrier defense and modulating visceral sensitivity and intestinal motility (Suzuki, 2020). Evidence suggests that breastfeeding may have protective effects on CVD, risk factors in adulthood compared with formula-fed (Rudnicka et al., 2007; Parikh et al., 2009), leading to small reductions in adolescent and adult blood pressure levels (Owen et al., 2003; Martin et al., 2004), decreased total cholesterol (about 0.18 mmol/L lower compared with bottle-fed) and low-density lipoprotein cholesterol levels (about 0.20 mmol/L lower compared with bottle-fed) in adulthood (Owen et al., 2002; Martin et al., 2005). This protective effect elicited by HM at the cardiac level has been confirmed by studies in animal models. Indeed, in HM-fed rats compared with control animals, increased cardiac antioxidant defenses, such as catalase activity (about 1.3 vs. 0.7 U/g tissue) and reduced levels of malondialdehyde (about 2.3 vs. 3.1 μmol/mg proteins) were observed (Trinchese et al., 2021). Malondialdehyde is an important marker of lipid peroxidation, and its increased levels are considered the first step on the way to the development of CVD (Halliwell, 2000). These observed positive effects were attributed at least in part to substantial PUFA n-3 content in HM (Koletzko et al., 2011).

COMPOSITION OF COW MILK

Cow milk has a long tradition in human nutrition, and it is one of the most-consumed drinks in the world. Indeed, 83% of worldwide milk production is dominated by cow milk (Bittante et al., 2022). Cow milk contains macronutrients and minerals, vitamins, and important bioactive compounds, whose abundance is influenced by different factors, such as genetics, health, lactation stage, and animal nutrition. Compared with HM and DOM, the protein content of CM is characterized by a higher casein-whey-protein ratio, making it less digestible (see Table 2). Casein represents approximately 80% of the total protein in cow milk. It is a heterogeneous family of proteins. There are 2 major variants for β-CN in CM: A1 and A2. The A1 casein variant has been implicated as a potential etiological factor in various human pathologies, including ischemic heart disease, diabetes mellitus-1, and autism, whereas the A2 variant has been found to be beneficial for human health (Kamiński et al., 2007; Chia et al., 2017). Furthermore, it contains a high level of β-LG, considered to be one of the major allergens responsible for allergy in infants (de Jong et al., 2022). Cow milk fat is composed of fatty acids of various chain lengths, most of which are SFA with a lower amount of MUFA and PUFA than HM and DOM (see Table 2). The main PUFA in milk are LA and ALA. The ratio between LA and ALA concentrations is an indicator of the nutritional effect of milk fat on human health and is greatly influenced by the feeding regimen. Also, CM is a source of CLA, which is a group of positional and geometric (*cis* or *trans*) isomers of LA with a conjugated double bond. The most representative CLA isomer is 9c,11t-18:2. Conjugated LA have been shown to exert various potent physiological functions on human health. The CLA isomer 9c,11t-18:2 in cow milk originates from 2 sources. A small fraction derives from the incomplete biohydrogenation of LA in the rumen that is absorbed from the small intestine and carried to the udder and included in the fat synthesis. Most of the CLA isomers originate from vaccenic acid, which is an intermediate in the biohydrogenation of UFA in the rumen. Following the absorption process, some of the vaccenic acid is desaturated in the udder by CLA delta-9-desaturase. There is a close positive correlation between the milk content of vaccenic acid and 9c,11t-18:2 CLA (Kay et al., 2004) and, moreover, between the milk content of CLA isomers and the dietary intake of LA and ALA, abundantly present in fresh grass (Kepler et al., 1966). Several studies have placed particular emphasis on the importance of animal feed in the composition of milk. Pasture feeding has been shown to have a positive impact on the nutritional profile of milk, increasing the content of some beneficial nutrients such as ALA and CLA isomers (Alothman et al., 2019; Mollica et al., 2021). High levels of ALA occur in fresh pastures and the fodder part of corn silage, whereas LA predominates in corn silage, cereals, and other oilseeds (Dannenberger et al., 2005). Diet is critical for the fatty acid profile of CM (Sterk et al., 2011); in particular, forage:concentrate (**F:C**) ratio in animal nutrition is determinant. Indeed, studies have shown that feeding dairy cows with a high F:C (70:30), results in a milk with a low n-6/n-3 ratio and high CLA levels (1.98 and 0.79% total fat, respectively), compared with feeding dairy cows with a low F:C (55:45; 6.96 and 0.45% total fat, respectively; Cavaliere et al., 2018). Further, by increasing the forage portion in the diet of cow's dairy, the following has been noted: a significant decrease of LA, a higher level of ALA and of total CLA, and a n-6/n-3 ratio close to 1 in milk (Benbrook et al., 2018). Also, other studies have shown that CLA content in milk produced on pasture feeding is at least twice than the one obtained by indoor feeding (Ledoux et al., 2005). Cow milk contains a wide range of minerals and vitamins. It is an important source of calcium and vitamins E and A, which play an important antioxidant role, along with the mineral selenium (Claeys et al., 2014). See Table 2 for a comparison of the CM component with those of the other milks examined.

METABOLIC EFFECTS OF COW MILK

The consumption of CM and cow dairy products is a dominant dietary characteristic in many cultures worldwide, especially in western communities. Indeed, milk is consumed by over 6 billion people. Fats from milk and dairy products are an important source of nutrients and energy. But the inclusion of a high proportion of milk and milk products in the human diet becomes questionable because of the health risk including cardiovascular risk. This is probably due to the high content of SFA present in milk, which are known to increase low-density lipoprotein cholesterol levels, a recognized risk factor for development of coronary heart disease (Dewhurst et al., 2003; Marangoni et al., 2018). On the contrary, in epidemiology studies carried out on large number of individuals from different countries, it was shown that total fat and types of fat introduced are not associated with CVD. Also, the intake of SFA appears inversely related with stroke. In addition, dairy consumption was correlated with lower risk of mortality and major CVD events (Dehghan et al., 2017, 2018). However, to date, a considerable number of studies have investigated the relationship between CM consumption and metabolic diseases, showing positive effects of milk and dairy intake. Some research has shown that a dietary pattern characterized by increased consumption of milk and dairy products, improve insulin resistance syndrome in overweight adults and may decrease the risk of type 2 diabetes (Pereira et al., 2002; Thorning et al., 2016; Jiang et al., 2022). Other studies associated the consumption of CM with beneficial cardiometabolic outcomes (Samuelson et al., 2001; Ricci-Cabello et al., 2012) and positive effects on brain function (Mollica et al., 2021; Arnoldussen et al., 2022).

The beneficial effects observed are attributable to the bioactive molecule content (Pereira, 2014; Mollica et al., 2021), such as fatty acid content, mainly n-3 PUFA and CLA. The n-3 PUFA exert beneficial effects on human health (Nguyen et al., 2019), participating in the inflammatory cascade, reducing oxidative stress (Lionetti et al., 2014a,b) and playing a protective role in the cardiovascular and nervous systems (Haag, 2003; Mata López and Ortega, 2003; Cavaliere et al., 2016). Several studies have shown several beneficial effects on inflammation, obesity, diabetes, and cancer, exerted by CLA isomers (Mollica et al., 2014; Kim et al., 2016; Trinchese et al., 2020). The content of n-3 and CLA in CM is closely associated with the animal feeding system. As reported above, fresh pasture feeding has been demonstrated to increase milk production in n-3 PUFA and CLA as compared with concentrated diets. In particular, n-3 PUFA and CLA are higher in CM fed with the higher F:C ratio (70:30) compared with CM fed with the low F:C ratio (55:45; n-3 PUFA: 1.21 vs. 0.32; CLA: 0.79 vs. 0.45% of total fatty acids; Cavaliere et al., 2018; Musco et al., 2020). Studies showed that milk from bovines fed with a different F:C ratio exhibit a different metabolic effect when administered in animal models. Specifically, rats treated with a dietary supplementation of milk from cows fed with a high F:C ratio (70:30) showed beneficial effects on lipid metabolism, inflammation, oxidative stresss, and antioxidant and detoxifying defenses by modulation of mitochondrial efficiency in the liver and skeletal muscle, compared with rats supplemented with milk from cows fed with a low F:C ratio (55:45; Musco et al., 2016; Cavaliere et al., 2018; Trinchese et al., 2019). In detail, regarding the lipid metabolism was observed an increase in the mitochondrial respiration rates in the presence of the lipid substrate palmitoyl-carnitine in the liver and skeletal muscle of rats treated with milk from cows fed with a high F:C ratio compared with ones treated with milk from cows fed with a low F:C ratio (liver: about 100 vs. 90 ng-atoms of O/min per mg of protein, respectively; skeletal muscle: about 300 vs. 250 ng-atoms of O/min per mg of protein, respectively). It was also observed a reduction in inflammatory parameters such as serum levels of interleukin-1 (40 vs. 60 pg/mL) and in oxidative stress parameters such as malondialdehyde in skeletal muscle (about 10 vs. 18 μM/mg proteins). Furthermore, an increase in parameters of antioxidant defenses, in rats fed with high F:C ratio compared with rats fed with milk at low F:C ratio was observed (e.g., about 18 vs. 12 nmol/mg per min of glutathione levels). Further studies carried out in animal models showed that dietary supplementation with butter rich in rumenic acid or vaccenic acid, both CLA isomers, showed a reduction in development of breast cancer, antiatherogenic effects and the reduce total plasma cholesterol level compared with standard butter-fed animals (7.41 vs. 10.82 mmol/L; Belury, 2002; Lock et al., 2005). Always on the animal model, it was observed a reduction in metabolic inflammation and an improvement of the intestinal protective function following diet supplementation with dairy cream from pasture cows than standard dairy cream in mice (Benoit et al., 2014). In detail, in adipose tissue of animals fed with pasture dairy cream compared with animal fed with standard dairy cream, a reduction in the inflammatory marker's expression was observed, such as IL-6 (0.6 vs. 0.8 arbitrary units), MCP-1 (0.05 vs. 0.15 arbitrary units), and TNF-α (0.3 vs. 0.45 arbitrary units). In dairy cream from pasture-fed compared with standard-fed animals, an increased number of cells involved in strengthening the protective function of the intestinal barrier such as goblet cells (15 vs. 10 number cells/crypts) was observed.

COMPOSITION OF DONKEY MILK

Donkey milk has historically been considered a food with therapeutic properties, and it has been used since antiquity for cosmetic purposes, as well as for infant and elderly nutrition (Bertino et al., 2022). The properties of DM differ from that of other mammals in many ways including important differences in nutritional value. To date, a growing number of investigations on the composition of DOM have revealed marked similarities to HM, especially in terms of its protein profile and lactose content. Donkey milk is a food rich in water and has a lower DM content than HM and CM, (water: 90.4, 87.6, and 87.6%, respectively; DM: 88–117, 107–129, and 118–130 g/L, respectively). Donkey milk total protein content is low compared with ruminant milk, and is very similar to HM, as reported in Table 2. In addition, a similar protein fraction profile was also observed between DOM and HM: indeed, both milks are characterized by a low casein content compared with CM, see Table 2. The β-CN is the main fraction in both DOM and HM (Derdak et al., 2020), whereas the other casein fractions are found at very low levels, and α_{S2} is absent in HM (Claeys et al., 2014; Cosenza et al., 2019). The protein fraction of caseins is the main allergenic components of milk (El-Agamy, 2007); thus, the low caseins content may explain the reduced allergenicity observed for DOM. In contrast, similar to HM, the protein fraction of DOM is particularly rich in whey protein, which has shown multiple beneficial metabolic properties (Mignone et al., 2015). The 3 main whey proteins of DOM are α-LA, β-LG, and lysozyme. Several studies have shown that α-LA has antiviral, antitumor, and anti-inflammatory properties (Yamaguchi et al., 2009). One of the main allergenic proteins in newborns and children is β-LG, which is the major whey protein in CM (Sélo et al., 1999), whereas it is absent in HM (Picariello et al., 2019). In DOM the content of β-LG is similar to that in CM (3.2–3.7 vs. 3.2–4.0 g/L, respectively; Claeys et al., 2014). Recent studies have shown that DOM β-LG is more digestible than CM (Tidona et al., 2014). Protein digestibility is important because food protein allergenicity is linked to the survival of the allergen in the gastrointestinal tract (Dupont, 2015). This condition may be associated with the hypoallergenic characteristic of DOM (Vincenzetti et al., 2014). Donkey milk contains a high amount of lysozyme, which in HM is found in lower concentration and in CM is almost absent (1.0, 0.04–0.2 g/L, and trace in DOM, HM, and CM, respectively; Claeys et al., 2014; Vincenzetti et al., 2017). Lysozyme is known to be a natural antimicrobial agent, reducing the incidence of gastrointestinal infections (Rubio, 2014), and exerting selective action on gut bacteria (Yvon et al., 2018). The lactose content of DOM is similar to that of HM and is much higher in comparison with CM (58–74, 63–70, and 44–66 g/L, respectively; Guo et al., 2007). The high lactose content is responsible for the good palatability of DOM. Recent studies have shown that sialylated oligosaccharides were found to be the main oligosaccharides in DOM, consisting of 3′-sialyllactose and 6′-sialyllactose, the amount of which are about 18.3 and 33.1 mg/L, respectively (Wang et al., 2019). Donkey milk contains oligosaccharides in amounts similar to CM (about 0.03–0.06 g/L) and lower than HM (about 7–12 g/L; Altomonte et al., 2019 Licitra et al., 2019). The primary difference between DOM and HM is the fat content, which is lower in DOM than HM (3–18 vs. 21–40 g/L), resulting in a reduced energy content (1,607–1,803 vs. 2,843 kJ/L; Claeys et al., 2014 Altomonte et al., 2019). The levels of LA and ALA in DOM (6–15.2 and 4–16.3% of total fatty acids) are higher than milk from ruminant species, such as CM (1.2–3.0 and 0.3–1.8% of total fatty acids; Gastaldi et al., 2010). Donkey milk has an PUFA content higher than that one found in HM (14.2–30.5 vs 8.1–19.1% of total fatty acids) and also a higher content of eicosapentaenoic acid (0.26 vs. 0.02 g/100 g of fat; Gastaldi et al., 2010), very important for human health, because they provide benefits for primary and secondary prevention of CVD (Adkins and Kelley, 2010). However, the docosahexaenoic acid content in DOM is about 50% lower than the mean values reported in HM (0.28 vs 0.40 g/100 g of fat; Gastaldi et al., 2010).

The vitamin content in DOM is quite similar to HM. In particular, DOM is rich in vitamin C (about 2,000 μg/100 mL), but poorer in vitamin A and E compared with HM and CM (vitamin A: 1.7 vs. 30–200 and 17–50 retinol equivalent; vitamin E: 5.1 vs. 300–800 and 20–184 μg/100 mL, respectively). Among the B complex vitamin, the most present in DOM are vitamin B1 and vitamin B2, whose content is higher than HM, but lower compared with CM (vitamin B1: 21–60 vs. 14–17 and 28–90 μg/100 mL; vitamin B2: 30–97 vs. 20–60 and 116–202 μg/100 mL, respectively; Claeys et al., 2014). Also, the mineral content in DM is closer to HM except for higher levels of calcium (33–115 vs. 28–34 mg/100 mL, respectively) and phosphorus (32–73 vs. 14–43 mg/100 mL, respectively) (Claeys et al., 2014). See Table 2 for a comparison of the DOM component with those of the other milks examined.

METABOLIC EFFECTS OF DONKEY MILK

In recent years, several studies have been conducted to clarify the composition of DOM. The presence of bioactive compounds has been identified, such as PUFA and n-3 fatty acids (Massouras et al., 2017), and functional proteins (Martini et al., 2019), responsible for the numerous beneficial effects observed on human health. Well known among the benefits found, is DOM's antioxidant ability, tested both in vitro and in animal models. Bioactive compounds in DOM appear to be involved in the elimination of hydroxyl radicals, superoxide anions (Li et al., 2017) and inhibition of lipid peroxidation (Zenezini Chiozzi et al., 2016). Rats treated with this milk showed an improvement in antioxidant defense mechanisms and detoxifying enzyme activity (Lionetti et al., 2012; Trinchese et al., 2018; Li et al., 2020). Specifically, DOM intake was found to increase superoxide dismutase activity, an important antioxidant system, in the plasma of diabetic rats compared with untreated animals (265.87 vs. 193.20 U/L; Li et al., 2020). In addition, administration of DOM in rat models fed a basic diet has been shown to improve the antioxidant status and cytoprotective enzymatic activities in serum and liver tissue. These beneficial effects on the pro-oxidant status observed can be attributed to the low n-6/n-3 PUFA ratio detected in this milk (Lionetti et al., 2012; Trinchese et al., 2015). Additionally, the administration of kefir from DOM in mouse models of Ehrlich ascites carcinoma decreases the NO synthesis, a marker for oxidative stress (Esener et al., 2018). Several studies have identified the anti-inflammatory effects of DOM, which at least in part, are attributable to the activation of the Nrf2 pathway (Lionetti et al., 2012) and its high levels of antimicrobial peptides (Yvon et al., 2018). The low cholesterol and fat content in this milk may make it favorable for patients with cardiovascular conditions (Tafaro et al., 2007). Indeed, thanks to the presence of n-3 fatty acids, a regular intake of DOM plays a protective role for cardiovascular districts, preventing the formation of atherosclerotic plaques (Bertino et al., 2022). Evidence is emerging that DOM plays a beneficial role in obesity and diabetes, due to its hypolipidemic effects related to its role played in modulating liver and muscle mitochondrial functionality, in turn responsible for improving lipid and glucose metabolism (Lionetti et al., 2012; Trinchese et al., 2015, 2018). Donkey milk was also found to have positive effects on glucose metabolism in rats with streptozocin-induced type 2 diabetes, in which a dietary supplement of DOM powder reduced blood glucose levels and insulin resistance. In detail, the levels of glucose in rats treated with DOM compared with diabetic rats are 14.23 versus 22.18 mmol/L, whereas the insulin levels are 17.19 versus 16.29 mU/L. The antidiabetic effect observed was similar to metformin therapy in most biochemical parameters (Li et al., 2020). Many studies have demonstrated the positive effects of DM on intestinal inflammatory disorders. Specifically, it has improved colon damage and colon mucosal inflammation in mice by enhancing the immune barrier function and promoting probiotic growth (Jiang et al., 2018).

Donkey milk consumption also restores endogenous antimicrobial peptide levels and fecal microbiota profile in a mouse model of Crohn's disease (Yvon et al., 2018). Many studies have reported that oligosaccharides present in this milk play an important role in developing and maintaining bowel health (Wang et al., 2019). Additionally, the ability of HM to modulate gut microbiota by affecting the proportion of bacterial phyla and genera and increasing the butyrate intestinal concentration that is well known to exert positive effects on intestinal health (Trinchese et al., 2015; Zou et al., 2019).

THREE TYPES OF MILK: SUMMARY OF PROS AND CONS

Human milk is the first option of infant feeding, an important source of nutrients for the newborns, able to provide the best opportunities for growth and development. It is a complex biological system rich of variety bioactive molecules, involved in multiple positive effects (e.g., protection against infections, the maturation of the gut microbiota and the nervous system development), contributing to short- and long-term health outcomes. Therefore, it has been widely recognized as valuable food, highly recommended during the first 6 mo of life. (Kunz et al., 2000; Kuntz et al., 2008; Agostoni et al., 2009; Pisa et al., 2021). To date it is not possible to find adverse effects related to the intake of HM. Cow milk accounts for 83% of global milk output and is a complete and easily available food. Indeed, it is used as a substitute for HM if the latter is not available. But it contains a high level of β-LG, the main allergen responsible for allergy in infants, which makes it unsuitable for children with CM protein allergies (de Jong et al., 2022). The introduction of milk and dairy products in human diet is questionable, duo to high content in SFA, which are known to increase low-density lipoprotein cholesterol levels, a risk factor for development of CVD (Dewhurst et al., 2003; Marangoni et al., 2018). On the other hand, several studies have shown an inverse correlation between the SFA content in milk and dairy products and adverse cardiovascular effects (Dehghan et al., 2017, 2018). In addition, the beneficial effects of CM intake on observed cardiometabolic outcomes are also attributed to the content of bioactive molecule, n-3 PUFA and CLA (Pereira, 2014; Mollica et al., 2021). The DOM composition is more similar to HM compared with CM. Furthermore, thanks to its palatability and to the low caseins and other proteins levels, it is particularly suitable for children suffering from CM protein allergy (Mignone et al., 2015; Vincenzetti et al., 2017). It contains various biomolecules that performs important functions: antimicrobial activity, (for example lysozyme and lactoferrin), anti-inflammatory actions and involved in the growth of gut microbiota (Rubio, 2014; Yvon et al., 2018). All these features make this milk an adequate alternative to HM, mostly for infants with CM protein allergy. The DOM is characterized by a low-fat content, resulting in a reduced energy content compared with HM (Altomonte et al., 2019), which could make it unsuitable for children at risk of malnutrition. To date, the biggest downside of DOM is its price and availability due to both limited number and size of donkey dairy farms.

CONCLUSIONS

In recent years, there has been an increasing emphasis on the relationship between nutrition and health, researchers have been encouraged to pay particular attention to analyzing both composition and quality of foods. In this context, milk plays an important role, as it is the first food used by newborns, to which it provides nourishment and growth. In addition, it is also used in adulthood by a large class of individuals as food. Several components positively affect human health through various interactions. In this review, we examined the major compositional differences between HM, CM, and DOM and reviewed the evidence supporting the main metabolic effects of certain bioactive components on human health. In the light of what reported, it is possible consider that the metabolic effects of milk on human health are closely related to its composition and quality.

The factors involved in defining the composition and quality of a type of milk are many. The beneficial effects of one type of milk over another are not attributable to a single constituent, but to a wide range of interacting factors, making it suitable for human health and even more for a specific target of individuals.

We believe that this review could be useful to get a general overview of the composition of the 3 types of milk examined and their main metabolic effects. However, to date, there are few studies in which all 3 types of milk have been compared at the same time. A major limitation of this review may be the lack of studies comparing the metabolic effects of the 3 types of milk in humans, given the absence of clinical studies. Although many studies have been made in this area, further insights are needed to clarify the underlying mechanisms linking the beneficial effects and the interaction of different constituent that characterize the different type of milk.

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