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Review

Donkey milk as a supplement in infant formula: Benefits and technological challenges

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ABSTRACT

The aim of this review paper is to assess the applicability of donkey's milk to infants suffering from Cow Milk Protein Allergy (CMPA) compared to human and other available milk types. The bioactive and immune-supportive character which could be beneficial as a fortifier to the formula-fed infants is described while limitations of this type of milk are also discussed. Studies showed that human and donkey's milk have similar, overall, chemical composition as well as protein homogeneity and antigenic similarities. Several in vitro and in vivo studies showed that donkey's milk has nutraceutical and functional properties that can support immunity, alter metabolism and beneficially modify gut microbiota. Clinical studies illustrated that donkeys' milk is well tolerated (82.6%–88%) by infants. Finally, the effect that processing (i.e. thermal, non-thermal treatments, drying methods) has on donkey milk components is also discussed pointing out the need for minimally processing this type of milk.

1. Introduction

Breastfeeding is considered as the ideal food for an infant's normal and healthy body, immunity, as well as cognitive development. Experts on this area recommend that infants exclusively receive only breast milk for their first 6 months of life (WHO, 2015). However, exclusive breastfeeding will be nutritionally inadequate after the first 6 months of infant's life as it is estimated to provide up to half (or more) and up to one-third of nutrients/cal needed when the infant is 6–12 months old and 12–24 months old, respectively (WHO, 2015). The complementary feeding of the infant (in addition to breastmilk) should consist of a variety of foods including fish, pulses, fats and oils, fruits but also, non-human milk and dairy due to their richness in calcium, protein and B complex vitamins (WHO, 2009a). For the nutritional demands of an infant, bovine milk is nutritionally rich; it provides adequate amounts of calcium and other minerals, vitamins, proteins and energy (The British Dietetic Association, 2015). However, bovine milk is an important allergen causing IgE-mediated immune reactions (immediate within minutes) as well as non-IgE-mediated (believed to be via T-cells) immune reactions which both are associated to one or more bovine milk proteins (Campbell, 2014; Mori et al., 2017). The main allergens in bovine milk are primarily the caseins (the most important allergen is the casein as_1) (Polidori, Ariani, & Vincenzetti, 2015) and secondly the β-lactoglobulin and α-lactalbumin (Peeters, Herman, & Baeck, 2017). In human milk the protein β-lactoglobulin is absent, whereas is the major whey protein in most ruminant's milk and is considered as an important protein that contributes to CMPA (Polidori et al., 2015).

Cow's milk protein allergy (CMPA) is defined by WHO as 'a hypersensitivity reaction against bovine milk proteins by specific immunological mechanisms (Campbell, 2014). CMPA is the most frequent allergy caused by foods in early childhood in developed countries with a reported prevalence of 0.3% to 3.5% in < 5 years old children and 1 % > 5 years; the majority of cases occur at 6-12 months of life which is the period where the infants are introduced to bovine milk protein (Koletzko et al., 2012). Nonetheless there are situations where infants cannot be breastfed because mother's milk is not available or in short supply for several reasons and hence they can be exposed to bovine milk proteins earlier (0–6 months) (Marletta, Tidona, & Bordonaro, 2016). It is estimated that the CMPA resolution is 60–70% when children are around 2 years old and 80–90% when they reach their 3rd year of life (Daly, 2016). However, few studies have recently reported that CMPA have become a long-lasting problem in children; i.e. the resolution rate is low (Del Giudice et al., 2015). The prevalence of IgE-mediated CMPA (depending on age and population) increases, ranging from 2% to 7% of the formula-fed infants; nonetheless it should be noted that the non-IgE mediated reactions are significantly more common than IgE-mediated immune reactions (Campbell, 2014). That indicates the relevance of CMPA in infants'.

Abbreviations: CMPA, Cow's Milk Protein Allergy

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Infants can directly be exposed to bovine milk protein (i.e. when introduced to bovine milk on infant formulas containing bovine milk proteins), or indirectly by breastfeeding because of the presence of bovine milk antigens found in the breast milk of lactating mothers who are drinking bovine milk (Ronzio, 2003). Some researchers have reported that native bovine proteins such as β-lactoglobulin can be transferred from the maternal bloodstream to breast milk but others point to cross-reactivity between human milk proteins and cow's milk proteins (Picariello et al., 2016). However, at the moment, no study has been able to correlate unequivocally the presence of these allergens in human milk with new-born sensitization (Restani et al., 2000). Mothers who consume > 950 mL of bovine milk daily will result in the passage of bovine milk protein antigens into human milk and hence expose the infant to these antigens at a very early stage of life (Ronzio, 2003); nonetheless, it should be mentioned that its highly unlikely that such a quantity of milk could be consumed on a daily basis. In general, breastfeeding mothers should avoid food sources with bovine milk protein too (Apps & Beattie, 2009; Daly, 2016; Koletzko et al., 2012).

2. Cross-reactivity between milk proteins from different animal species

Nonetheless, CMPA infants are not affected only by bovine milk proteins. Milk from different ruminants may show cross-reactivity in CMPA infants. For instance cross-reactivity between milk proteins of different ruminants and humans can occur when they are capable of binding to specific antibodies due to their molecular structure, or when they share part of their amino acid sequence (Park, 2009). Indeed, it is documented that there is high homology (87–96%) in the amino acid sequence of milk proteins of bovine, ovine and caprine milk as well as in their ratio of caseins and whey proteins. Due to these similarities, most of the CMPA infants show an IgE mediated cross-reactivity between caprine, bovine, buffalo and ovine milk; 93–98% of IgE-mediated CMPA infants show cross-reactivity to caprine and ovine caseins. Both in vitro and in vivo studies have shown this extensive cross-reactivity. As a result, milks from other ruminants such as caprine and ovine are not considered safe alternatives to bovine milk in CMPA infants based both in vitro as well as in vivo studies (D'Auria, Mandelli, Ballista, Di Dio, & Giovannini, 2011; Nagaraju, 2013; Polidori et al., 2015).

3. Plant-derived proteins: cross reactivity and other issues

In addition to sensitisation to other ruminants milk, CMPA infants shows cross-reactivity to soy proteins too, hence, classifying soya bean proteins as an unsafe alternative to bovine milk proteins; approximately 17–47% of CMPA infants show cross-reactivity between bovine milk proteins and soy proteins (Nagaraju, 2013; Shek & Allen, 2016; Uniacke-Lowe & Fox, 2012). However, there is another reason (other than allergic reactions) why soy infant formula is not recommended to infants and young children. Soy infant formula contains soy protein and other components i.e. isoflavones. This is a class of compounds that are naturally found in legumes and beans, including soybeans. Among the isoflavones found in soy formulas, genistein, daidzein and at lower levels glycitein, are the major compounds. These isoflavones are known as phytoestrogens due to their estrogens-like activity in the body. There are stages in infant's development that are affected by estrogens and hence, compared to adults; infants have higher probabilities of being affect by phytoestrogens (Strom et al., 2001). In addition, infants or toddlers are more likely to being affected than adults because infants diet at that stage of life, i.e. at the beginning of the complementary feeding (> 6 months old), is primarily represented of breast milk and the infant formula and other foods. Infants that are solely fed soy formula because they cannot be breastfed and suffer from CMPA, are exposed to much higher doses of soy phytoestrogens than older children or adults who consume a variety of foods in their diet. It is reported that in certain cases, problems associated to the exposure to soy formula at that stage of life may take years to develop and show symptoms (Strom et al., 2001). Examples of potential health issues derived from animal studies include earlier puberty in females and reduced fertility in males (National Institute of Environmental Health Sciences, 2016; WHO, 2009a). In addition to the phytoestrogens, other components in soya can cause harm e.g. phytates which could affect iodine metabolism (D'Auria et al., 2011). As a result, hydrolysed milk formulas and amino acid formulas are preferred compared to soy infant formulas (National Institute of Environmental Health Sciences, 2016). Between extensively hydrolysed milk formula (eHF) and soy formula, the use of eHF in order to avoid adverse reactions is suggested (Fiocchi et al., 2010). Preferably CMPA infants are fed eHF or amino acid formula (AAF) for their first year of life; soy formula could be introduced after that period (Daly, 2016).

Rice formula has been shown that can provide adequate nutrients for similar growth compared to eHF and is tolerated by the CMPA infants (D'Auria et al., 2011). However, rice milk may be provided after the age of 5 due to the levels of arsenic in rice milk. High concentrations of arsenic in rice-based infant formulas have been reported (Abedin, Cotter-Howells, & Meharg, 2002; Hernández-Martínez & Navarro-Blasco, 2013; Jackson, Taylor, Punshon, & Cottingham, 2012). Other milks such as hemp, oat, pea, coconut or almond milk are not recommended under 2 years old (The British Dietetic Association, 2015). A study has shown that infant formulas that are non-dairy (in that study included soy-based and rice-based formulas), had significantly higher arsenic content than infant formulas that are dairy-based (Jackson et al., 2012).

4. Infant formulae

The infant population with CMPA is fed either eHF or AAF, depending on the severity of the CMPA case (Koletzko et al., 2012). The eHF is made of bovine milk and the milk proteins are less recognisable by the immune system since they are broken down in smaller peptides by hydrolysis (Daly, 2016). However, the eHF contain residual allergic epitopes that can be recognised by the immune system and cause allergic reactions (Del Giudice et al., 2015; Polidori et al., 2015). On the other hand, in an AAF no proteins or peptides exist; hence amino acids are not recognisable by the immune system as there are no residual allergic epitopes present (Daly, 2016; Del Giudice et al., 2015). For children who are suffering from IgE-mediated CMPA but are at low risk of anaphylactic reactions, are recommend to use eHF instead of an AAF. On the other hand, children with IgE-mediated CMPA are known to have high risk of anaphylaxis, experts suggest the use of AAF instead of eHF (Daly, 2016; Fiocchi et al., 2010). It is reported that approximately 10% of CMPA children cannot tolerate the (eHF) and hence consume amino acid formulas (Apps & Beattie, 2009).

The reason AAF is not recommended in the group of infants with low risk of anaphylaxis is because of the substantially higher cost; hence in low risk of anaphylaxis the parents have the flexibility of using the eHF (Fiocchi et al., 2010). The amino acid infant formula is the first choice when hydrolysed milk formulas cannot be tolerated and the CMPA infant is at high risk of anaphylaxis (D'Auria et al., 2011; Del Giudice et al., 2015; Koletzko et al., 2012). However, it should be stated that both eHF and AAF have organoleptic drawbacks which makes them unacceptable by the infant i.e. unpleasant flavour and bitter taste, respectively. (Del Giudice et al., 2015; Polidori et al., 2015).

To conclude, it is reported that in general 25–80% of CMPA infants cross-react with infant formulae which contains soy, ovine or caprine milk or even hydrolysed milk (Swar, 2011). As it will be described below, based on the current knowledge, it appears that monogastric animal's milk is more suitable to humans rather than the ruminant's milk (Trinchese et al., 2015).

Table 1
Clinical studies on the effect of donkey milk in the treatment of Cow Milk Protein Allergy (CMPA) in children.

Symptoms	Sample population	Age	Other treatments	Donkey milk	Reference
Severe symptoms of cow's milk allergy- Diarrhoea, abdominal pain, vomiting and growth retardation	9 unweaned infants with multiple food hypersensitivity	0–3 months	Milk containing soy protein or a semi elemental formula No improvement in their clinical condition	Donkey milk (250 mL/kg/day) supplemented with medium chain triglycerides (MCT) (40 mL/L milk) No negative clinical reactions- average weight increase was 39.8 g/day	Iacono et al., 1992
Diarrhoea, abdominal pain, vomiting	Group A: 21 Hydrolysed Protein-intolerant infants treated with a donkey milk-based diet Group B: 70 cow's milk intolerant infants treated with casein hydrolysate milk-based diet	2–3 months	None of the patients showed intolerance to casein hydrolysed formula	Donkey milk 210–250 mL/Kg/day, supplemented with MCTs at a daily dose of 40 mL/L of milk 3/21 patients became donkey's milk intolerant; they showed vomiting (one cases) or diarrhoea (two cases). 52% of patients in the donkey's milk group became Cow's Milk-tolerant during the study period which is lower than in the casein hydrolysate group (78%)	Carroccio et al., 2000
Cutaneous symptoms (atopic dermatitis, urticaria/angioedema), gastrointestinal symptoms and growth retardation (poor weight gain)	46 CMPA children for whom maternal milk was not available and no available cow's milk substitute (soya formula, cow hydrolysed formula or amino-acid formula-AAF)	1–146 months	7 of the 46 children (15%) did not tolerate extensively Hydrolysed Formula (eHF) and refused ingestion of AAF, and the remaining 39 categorically and systematically refused to take either eHF or AAF.	200–500 mL/day depending on age Thirty-eight children (82.6%) liked and tolerated donkey's milk, whereas eight children (17.4%) showed hypersensitivity to donkey milk	Monti et al., 2007
Atopic dermatitis (AD)	28 children with AD and ascertained allergy; 2 drop out	6–36 months	23 of 26 children had a positive food challenge with Goat Milk	Donkey milk invariantly led to a significant improvement of SI and VAS of symptoms 1 of 26 showed hypersensitivity to donkey milk	Vita et al., 2007
Cutaneous (atopic dermatitis, urticaria/angioedema), gastrointestinal, and/or respiratory symptoms	25 CMPA children	6–11 months	Not determined	Donkey milk was tolerated by 24 out of 25 children. All children had an improvement of their weight and height	Tesse, Paglialunga, Braccio, & Armenio, 2009
Cutaneous symptoms (atopic dermatitis, urticaria/angioedema), gastrointestinal symptoms and growth retardation (poor weight gain)	92 children with CMPA	7.5–121.5 months	Not determined	83 children (90.2%) liked and tolerated donkey milk. All children had an improvement of their weight and height	Monti et al., 2012

5. The importance of donkey's milk to CMPA infants

Human milk is the ideal feed for infants, however, if unavailable, an alternative should be used; this becomes extremely challenging in infants suffering from CMPA. From the different ruminant and monogastric milk, donkey's milk is considered to be the best alternative to human milk for CMPA infants due to its palatability (as it has similar organoleptic characteristics to human milk), and clinical tolerability (Marletta et al., 2016; Monti et al., 2007, 2012; Murgia et al., 2016; Trinchese et al., 2015). The use of donkey's milk for feeding infants is not a recent practise, it dates back in 1881 in Paris were donkey's milk was use for feeding syphilitic children since donkeys couldn't be infected by syphilis (i.e. donkeys were impervious to syphilis infection) (Chiofalo, Drogoul, & Salimei, 2006). When breast feeding is unavailable and in cases of CMPA, the use of donkey's milk is recommended as an alternative solution (Polidori et al., 2015). Table 1 summarizes the clinical studies where donkey milk was used for the treatment of CMPA in children.

As it is described below donkey's milk is superior to ruminant's milk due to its similar composition to human milk, higher digestibility, higher tolerability by CMPA infants, its bioactive and anti-infective factors and potentially healthier impact on metabolism of infants compared to bovine milk. A recent study showed that the profile of metabolites found in human and donkey milk are similar in comparison with bovine milk-based infant formula (Murgia et al., 2016).

5.1. Donkey's milk allergenicity/tolerability in relation to the structure of its proteins

Many clinical studies indicated the high tolerability of donkey's milk by infants suffering from CMPA who were intolerant to extensively hydrolysed milk formula, soy protein based infant formula and even pure amino acid infant formula (Carroccio et al., 2000; Monti et al., 2012; Polidori et al., 2015). Some research characterised donkeys milk as a possible alternative to human milk (when human milk is unavailable) in children with CMPA (Martuzzi & Simonini, 2010; Polidori & Vincenzetti, 2012). Moreover, in a preliminary study carried out by Mori et al. (2017), suggested that donkey milk could also be a good alternative for children that suffer from bovine milk enterocolitis syndrome but more research is still needed.

It is reported that the low allergenicity of donkey's milk is related to its protein fraction (Bertino et al., 2010; Ling, 2007). As already mentioned, casein proteins of bovine milk are considered the major allergens that causes CMPA; αs1- and αs2- CNs represent the most important allergens (Polidori et al., 2015). Studies on donkey milk clearly demonstrate that donkey milk proteins (especially casein components) are more closely related with the human homologues rather than cow counterparts (Barłowska, Szwajkowska, Litwińczuk, & Król, 2011; Park, 2009). In particular αs1- and β-caseins in different phosphorylated forms has been shown to be present in large amount in donkey's milk; κ-casein and αs2-casein are also present although in very small amounts (Bertino et al., 2010; Vincenzetti et al., 2008). Moreover, the low allergenic properties of donkey milk with respect to cow milk seem to be related to the low total protein content, the low ratio of caseins to whey fraction, and finally to the presence in almost all bovine IgE-binding linear epitopes of multiple amino acid differences with respect to the corresponding regions of donkey milk counterparts (Bertino et al., 2010; Cunsolo et al., 2011, 2017; Uniacke-Lowe, Huppertz, & Fox, 2010). Donkey's milk as_1 casein is not only lower in quantity compared to bovine milk as_1 casein, but in addition, it has high heterogeneity due to variable degree of phosphorylation and to the presence of genetic variants (Vincenzetti et al., 2012). Moreover the low amount of as2-casein and kappa-casein in donkey milk could also contribute to its lower hypoallergenicity. Several other variations in the structure of casein proteins have been reported for donkeys milk which are also linked to the low allergenicity of donkey's milk (Marletta et al., 2016). Donkey milk αs1-CN and αs2-CN have a reduced tertiary structure and therefore their major allergenic epitopes are sequential rather than conformational. As already mentioned above, most of the amino acid sequences of the major allergenic linear epitopes of these two bovine caseins have remarkable differences with respect to the corresponding domains present in donkey counterparts (Cunsolo et al., 2017). Moreover, donkey milk shows two internally-deleted αs2-CN isoforms which don't present two phosphorylation sites and the unique disulphide bond present in the full-length isoform A (Vincenzetti, Pucciarelli, Polzonetti & Polidori, 2017). Therefore, elimination of phosphorylation sites may reduce IgE response to caseins and the absence of disulphide bonds may decrease the resistance to denaturation, the posttranscriptional events generating these two internally-deleted isoforms may contribute to the low allergenic properties of DM. Finally, there are stronger antigenic similarities in the whey proteins of human's and donkey's milk compared to other species (Barłowska et al., 2011; Park, 2009). The donkey whey proteins represent 35–50% of the nitrogen fraction, while in cow milk they are only 20%. The main components of whey proteins, as reported by Salimei et al. (2004) are represented by β-lactoglobulins (29.9%), α-lactalbumin (22.6%), lysozyme (21%), immunoglobulins (11.5%), serum albumin (6.2%), and lactoferrin (4.5%). Moreover, the quali-quantitative polymorphism at donkey β-Lg II locus highlighted the possibility that β-Lg could be expressed at low level in donkey milk and this, may affect its composition and therefore, its allergenic properties (Cunsolo et al., 2011).

5.2. Donkey's milk allergenicity/tolerability in relation to the digestibility and the ratio of individual proteins

Donkey's milk digestibility is higher than bovine's milk and similar to human milk, because of the high whey proteins content and the few casein content (Ling, 2007; Marletta et al., 2016). For example, the digestibility of β-lactoglobulin of donkey milk is very high compared to bovine milk; approximately only 30% of donkey's β-lactoglobulin remains undigested compared to bovine β-lactoglobulin which is 60% (Inglingstad et al., 2010; Marletta et al., 2016).

Comparing human milk with other mammalian milk (bovine, caprine, sheep, buffalo, yak, reindeer and camel), the human milk components differs in terms of ratios; the protein content is lower in human milk compared to that of ruminants but is very similar to that of donkey's and mare's milk (Barłowska et al., 2011; Park, 2009). Species such as humans and donkeys feed their young frequently and several times per day because their milk is relatively dilute with very low levels of caseins; usually < 60% of the total protein content (Uniacke-Lowe et al., 2010). There is low casein and high whey protein ratio but also lower total casein content in human's and donkey's milk (approximately < 30% and 35–45% of the total protein content, respectively) compared to ruminant's milk (> 70% of the total protein content) (bovine, buffalo and sheep) (Barłowska et al., 2011; Marletta et al., 2016; Park, 2009).

Despite the fact that it is not clear why donkey's milk can be tolerated by patients who suffer from allergies to bovine, ovine and caprine milk proteins, the ratio of casein to whey proteins in the milk appears to be an important contributor, too, as it was reported that a bovine milk with low casein to whey ratio wasn't as allergenic as the normal bovine milk with a high casein to whey ratio (Lara-Villoslada, Olivares, & Xaus, 2005; Polidori et al., 2015).

The lower allergenicity of the “low casein to whey ratio” could be attributed to the softer curd formed in the stomach. In the acidic environment (pH = 2–3) of the stomach, donkey's milk (just like human milk) due to the low total protein content and the low ratio of casein to whey proteins, forms a soft, fine and more easily digestible gel/curd (Claeys et al., 2014; Fiocchi et al., 2010; Marletta et al., 2016; Minekus et al., 2014). Bovine milk forms very dense and strong gels under acidic conditions due to the high concentration of casein in milk and the higher casein to whey ratio (Claeys et al., 2014; Fiocchi et al., 2010;

World Health Organization, 2009b). The strength of the gel formed under acidic conditions affects the subsequent degradation and digestibility of the proteins and hence the absorption of milk nutrients (Claeys et al., 2014; Marletta et al., 2016).

5.3. Donkey's milk bioactivity

5.3.1. Anti-infective factors

Infants who are breast-fed have lower incidence as well as less severe infections, and gastrointestinal illnesses compared to infants who are not breast-fed (Baldi, Ioannis, Chiara, Eleonora, & Roubini, 2005; Brundige, Maga, Klasing, & Murray, 2008). Human milk carries components that are crucial for treating or protecting the infant from infections such as lactoferrin, lysozyme and immunoglobulins (Ballard & Morrow, 2013; Lu et al., 2016; Maga et al., 2012).

In addition to its ability to directly protect the intestinal environment from pathogenic microorganisms, lysozyme is thought to contribute to the reduction of the number of facultative anaerobes and hence be partly responsible for the evidence-based superior intestinal microbiota (i.e. consisting mainly of staphylococci, lactobacilli and bifidobacteria and with reduced numbers of pathogens including campylobacter, *E. coli*, bacteriodes and streptococci) of breast fed infants compared to infants who are fed infant formulae which causes an unfavourable gut microbiome containing high numbers of clostridia, coliforms, streptococci, enterococci and bacteriodes (Baldi et al., 2005; Ling, 2007; Maga et al., 2012).

Due to the positive influence of lysozyme to the gut microbiota, it is suggested that a milk with high concentration of lysozyme can divert the microbiome of the gut of infants towards a microbiome that is linked to a healthy status; for example lysozyme favours the colonisation of bifidobacteria in infant's gut (Maga et al., 2012; Minami, Odamaki, Hashikura, Abe, & Xiao, 2015). Human's milk contains high concentrations of lysozyme (~0.37–0.89 mg/mL) whereas it is reported that the lysozyme content in ruminants milk is almost absent (Polidori et al., 2015). Indeed, bovine and caprine milk lysozyme content is 0.13 μg/mL and 0.25 μg/mL respectively (Maga et al., 2012). Interestingly, donkey's milk has a high lysozyme content (reported values range from 1 to 4 mg/mL) (Barłowska et al., 2011; Ling, 2007; Marletta et al., 2016; Massouras, Triantaphyllopoulos, & Theodossiou, 2017; Vincenzetti et al., 2012).

Despite the nutritional adequacy of infant formula, human milk provides superior advantages to the infant including reduced risk to infections due to the presence of bioactive proteins in the human milk such as lysozyme (Huang et al., 2002; Lönnerdal, 2016). Currently only infants who are fed human milk can receive these bioactive proteins (Lönnerdal, 2002). Due to the limited availability of human milk and the issues associated with formula-fed infants, the addition of lysozyme in infant's formula was investigated. The addition of lysozyme to infant formula may be important in growth or host defence and also for the reduction of allergies and gastroenteritis incidences (Ferrari & Feuerstein, 2007; Huang et al., 2002). In a study carried out by Zavaleta et al. (2007) it was demonstrated that the addition of lysozyme and lactoferrin to the World Health Organization (WHO) rice-based oral rehydration solution (ORS), have a beneficial effect in children hospitalized with acute diarrhoea. This is a clear indication of the impact that dietary interventions can have on health and immunity. However, since there are limited quantities of human milk lysozyme for isolation, there is now considerable interest in developing recombinant (genetically engineered/modified; transgenic production) sources of human milk lysozyme for use in infant formulas. For example, genetically modified plants (like rice) or animals (i.e. cows) can produce large quantities of lysozyme (Huang et al., 2002; Lönnerdal, 2002; Lu et al., 2016). Nonetheless, the use of products from genetically modified organisms can possibly raise parent's concerns over the applicability of these products to their new-borns.

Therefore, donkeymilk can be of particular interest for use in infant's formula or in conjunction to an infant balanced diet due to its exceptionally high lysozyme content, therefore providing to formula-fed infants some of the benefits of breastfeeding (Barłowska et al., 2011; Marletta et al., 2016; Vincenzetti et al., 2012). Approximately 75% of donkey's milk lysozyme remains intact after digestion by human gastrointestinal enzymes; this is particularly important since the presence of intact lysozyme in the stool of infants is believed to confer antimicrobial activity and modulation of microbiota in the gut of infants receiving breast milk (Lönnerdal, 2016; Marletta et al., 2016).

In addition, the whey protein fraction (which includes β-lactoglobulin, α-lactalbumin, serum albumin, lysozyme, immunoglobulins, lactoferrin and) from raw donkey's milk has strong antiviral properties in vitro (Brumini et al., 2013). Finally, a recent study showed that donkeys' milk can indirectly support immunity by enhancing Paneth cell mediated innate immunity (Yvon et al., 2016).

5.3.2. Metabolism

Several studies showed associations between the gut microbiota and health and disease (Maga et al., 2012). For example, gut microbiota is an important regulator of obesity (due to its ability in regulating fat accumulation) and consequently affects the diseases associated with obesity (Blandino, Inturri, Lazzara, Di Rosa, & Malaguarnera, 2016). Recently, based on observational studies in Western countries, the elevated consumption of bovine milk in the first months of infants life has been characterised as an important contributor to the elevated obesity (and other disorders) in early childhood (Agostoni, Baselli, & Mazzoni, 2013). In a recent study, Trinchese et al. (2015) investigated the impact of equicaloric supplementation of human, donkey and bovine milk on energy balance, oxidative stress, inflammatory state and enzymatic activity for antioxidant and detoxifying action and other metabolic functions in animal models. Unlike bovine milk, human and donkey milk were associated with improved glucose and lipid metabolism as well as the reduction of the inflammatory status in donkey milk-treated rats. Donkey and human milk showed an increase in energy expenditure and hypolipidemic effect together with an improved mitochondrial activity and proton leakage as well as a reduction of inflammatory status which was associated with improved metabolism of glucose and lipids (Trinchese et al., 2015). Moreover, donkey and human milk have a comparable ability in lowering the built up of lipids in the body and to upregulate fat utilisation for energy of hepatic mitochondria in animal models (Lionetti et al., 2012; Trinchese et al., 2015). It is stated that the benefits in metabolism after consumption of donkey or human milk are associated with alterations in the microbiome of the gut; changes in genera and phyla have been observed (Trinchese et al., 2015). This functional similarity of donkey and human milk could be associated with the higher lysozyme content of these milks compared to the marginal lysozyme quantities present in bovine milk (Maga et al., 2012; Polidori et al., 2015). In addition, the similar action of donkey and human milk on metabolism could be due to their qualitative and quantitative similarities in protein glycidic and lipid fractions, unlike bovine milk (Bertino et al., 2017). This could partly help explain why bovine milk-fed mice showed increased body lipid and body weight. Finally, donkey and human milk caused an increase in the detoxifying and antioxidant activities of enzymes (Trinchese et al., 2015).

5.3.3. Other bioactive compounds

In addition to the antimicrobial and gut modulating effect of lysozyme, several proteomic and peptidomic studies have identified constituents of donkey's milk that carry other bioactive properties (Cunsolo et al., 2017). For example, a whey protein fraction (whey proteins of molecular mass > 10 kDa) has shown to have direct as well as indirect anti-tumor action by activating macrophages and lymphocytes in vitro (Mao et al., 2009). Furthermore, digested samples of whey proteins from raw donkey's milk show very strong antioxidant activity similar to BHA and BHT antioxidants (Bučević-Popović, Delaš, Međugorac,

Pavela-Vrančić, & Kulišić-Bilušić, 2014). Other in vitro studies showed that donkey milk can stimulate nitric oxide production from human monocytes, the release of IL-12, IL-1β, IL-10 and TNF-α, IgG and IgA and hence maintaining immune homeostasis (Jirillo & Magrone, 2014). Moreover, a recent study found similar concentrations of pyroglutamic acid in human and donkey's milk compared to infant formula milk. It is suggested that pyroglutamic acid acts against diabetes since it is related to glycolysis regulation (Murgia et al., 2016). In addition, the concentration of myo-inositol is similar between human and donkey milk, in contrast to infant formula milk. Myo-inositol is crucial for the normal development of infants; it acts as an osmoregulator and also as a precursor of phospholipids (Murgia et al., 2016).

6. Preterm infants: donkey's milk as a new human milk fortifier

Human milk should be considered as the first choice for the nutrition of all infants, including preterm newborns. However, a very-low-birth-weight (VLBW) infant has increased needs and hence the energy, protein and mineral content of human milk are inadequate. For that reason, human milk is fortified when is intended for VLBW. The process of fortification of human milk is a critical intervention because it should meet the nutritional needs for normal growth of the newborn.

However, the commercial protein concentrates and multi-nutrient fortifiers are made of bovine milk which carries a very different protein composition compared to human milk. The bovine-derived milk proteins have recently received attention due to the possibility of being associated with intestinal inflammation in VLBW infants. In addition, in extremely premature new-borns, bovine milk-based fortifiers had higher necrotizing enterocolitis rates and higher mortality compared to human milk-based fortifiers.

Currently, due to the similar impact of human and donkey milk on the metabolism a clinical trial was carried out in order to assess whether the use of a protein concentrate and a multi-component fortifier, both derived from donkey milk, can have a different impact on the feeding tolerance, metabolic, clinical, auxological and neurological outcomes both in Very Low Birth Weight (VLBW) and gestational age < 32 weeks infants at short as well as long-term, compared to bovine milk-based fortifiers (Bertino et al., 2017).

Moreover, a randomized, controlled, single-blind clinical trial study is still running by Coscia et al. (2018) in order to evaluate feeding tolerance, growth and clinical short and long-term outcomes (clinical, metabolic, neurological or auxological) in a population of preterm and VLBW infants fed with a novel multi-component fortifier and a protein concentrate derived from donkey milk, in comparison to an analogous population fed with traditional fortifier and protein supplement containing bovine milk proteins.

7. The importance of a minimally processed-bioactive donkey's milk in infant's diet

Apart from the unavoidable allergenicity and poor palatability of extensively hydrolysed bovine milk proteins or soy milk proteins employed in infant formula, the bioactive and anti-infective factors are totally absent, despite the fact that today the infant formula contains a variety of ingredients to mimic the human milk (World Health Organization, 2009a). On the other hand, beyond the nutritional importance, human milk also carries bioactive and anti-infective components which beneficially affect the immunity, have anticancer properties, confers hormonal and pharmacological support, protects cardiovascular system and gastrointestinal health as well as improving recovery and development of new-borns intestine (Ling, 2007; Polidori et al., 2015). Even though there are protective factors, immunomodulatory, anti-oxidative and anti-bacterial activities in unprocessed bovine milk too, due to its extensive processing such as during hydrolysing the proteins to reduce their allergenicity, the bioactivity of these factors is significantly compromised (Ling, 2007; Wada & Lonnerdal, 2015). This observation could also help to explain why formula-fed infants are more susceptible to infections in comparison to breastfed infants (Ling, 2007). As a result, donkey's milk can be used as a hypoallergenic natural milk alternative for CMPA infants in conjunction to their diet or be used as a replacer of the protein source in infant formulas; i.e. as a replacer of extensively hydrolysed milk proteins or even amino acids (Polidori et al., 2015).

The characterisation of the microbiology and safety of donkey's milk is still at the very early stages of research and hence is unclear. Although there are examples of studies describing the absence of certain pathogen (i.e *Salmonella* spp. and *Listeria monocytogenes*) (Aspri, Bozoudi, Tsaltas, Hill, & Papademas, 2017), other studies report the presence of other pathogens such as *Staphylococcus aureus*, *Enterobacter sakazakii*, *Streptococcus equi*, *Streptococcus equisimilis* and *Brucella* spp. (Dalmasso, Civera, & Bottero, 2017; Malissiova et al., 2016; Pilla, Dapra, Zecconi, & Piccinini, 2010; Ragona et al., 2016; Sarno, Santoro, Di Palo, & Costanzo, 2012; Verraes et al., 2014). Therefore, the need of reducing the microbial load for safety is an unavoidable step which can compromise the bioactivity of the milk to a degree depending on the processing method employed. A recent paper published by Giacometti et al. (2016) investigated the effects of different treatments on microbiological indicators of donkey milk hygiene and their evolution during shelf life. Results showed that the most effective treatment to maintain microbiological donkey milk quality up to 30 days was pasteurization plus HPP. Moreover, treatment of donkey milk with UHPH was also able to maintain the microbiological quality of donkey milk up to 28 days (Addo & Ferragut, 2015). It proved also to have a positive effect on the lysozyme activity similar to pasteurization, maintaining the activity over the storage period. Donkey milk is considered as an innovative dairy food as it carries bioactive components with human-like activity which is suggested as being responsible for its ability to support human health (Salimei, 2010). Therefore, the novelty of adding donkey's milk in place of extensively hydrolysed bovine milk proteins or soy milk should not be assessed in terms of allergenicity and palatability only but should be based on the degree of the bioactivity of the finished product too, otherwise, the donkey milk based infant formula will only be a hypoallergenic, palatable alternative to extensively hydrolysed milk formulas. Indeed, as reported in a study, donkey milk can be considered as a valid alternative (when human milk is unavailable) to humans milk in CMPA infants when it can confer a number of biological functions similar to those with human milk (Polidori & Vincenzetti, 2012).

Donkey milk is considered as a valid alternative to CMPA infants due to its compositional similarities with human milk, proven clinical tolerability, palatability and adequacy in nutrients as well as its richness in bioactive compounds (Monti et al., 2012; Polidori et al., 2015; Polidori & Vincenzetti, 2012; Salimei & Fantuz, 2012).

8. The need for non-thermal processes

The major methods used for ensuring that the food is microbiologically safe as well as shelf stable are thermal processing methods; for the last 100 years or more, thermal processing is the most used method for preserving milk. When a food is thermally processed, in order to ensure safety as well as to avoid spoilage, the aim is to heat the food to a specified temperature/time profile required for the inactivation of foodborne and spoilage microorganisms as well as enzymes (Ashenafi, 2012). During thermal processing, microbial and enzymatic inactivation is achieved, in addition to certain other reactions, due to the denaturation of proteins as well as melting of certain food components. However, the thermal processing of foods results in undesirable and unavoidable changes too, including organoleptic changes but most importantly loss of nutritional value as well functionality of valuable enzymes due to denaturation (Ashenafi, 2012). Low Temperature Long Time (LTLT; 62–65 °C for 30 min followed by immediate cooling to $<$ 10 °C), High Temperature Short Time (HTST; 72–74 °C for 15–30 s) and

Table 2
Effect of processing treatments on donkey milk constituents.

Treatments	Donkey milk constituents			Reference
Effect of temperature	Lysozyme	β-Lactoglobulin	Lactoferrin	
65 °C	No significant effect	No significant effect	50% decrease	Ozturkoglu-Budak (2016)
75 °C	Limited loss (8.25%)	No significant effect	Disappeared	
85 °C	Loss of stability-60% decreased	Loss of stability-87% decreased	Disappeared	
−20 °C	No significant effect	No significant effect	Small loss	
4 °C to 50 °C	No effect	nd	nd	Polidori and Vincenzetti (2010),
70 °C	50% decrease	nd	nd	Polidori and Vincenzetti (2013)
−20 °C	No effect	No effect	nd	
63 °C/30 min	Small decrease (6.6%)	nd	nd	Giribaldi et al. (2017)
72 °C/15 s	Small decrease (5.5%)	nd	nd	
70 °C/1 min	No significant effect	nd	nd	Addo and Ferragut (2015)
85 °C/1 min	No significant effect	nd	nd	
Effect of drying				
Spray-drying	30% residual activity	No effect	nd	Polidori and Vincenzetti (2010), Polidori and Vincenzetti (2013)
Freeze-drying	No significant effect	No significant effect	nd	Vincenzetti et al. (2018)
Spay-drying	Significantly decrease of lysozyme enzymatic activity (58% of residual activity)	Small loss- β-lactoglobulin content (6.43 mg/mL in fresh milk vs 5.51 mg/mL in spray-dried milk)		
Effect of homogenisation				
Ultra High Pressure Homogenisation (UHPH)- 100, 200, 300 MPa	No significant effect	nd	nd	Addo and Ferragut (2015)

nd = not determined.

Ultra-high Temperature (UHT; 135–140 °C for 2–5 s) are the most common thermal processes employed for milk processing (Ashenafi, 2012).

As donkey milk is an expensive product with a well-documented bioactive character, the available literature discussing the impact of various processing methods on human milk are of utmost importance for reasons including the similarity in the composition of the two milk types and the intended use in infant diet. Several studies on human milk as well as other types of milk has shown that heat treating the milk results in reduction of the bioactive components (Ballard & Morrow, 2013; Bertino et al., 2015; Gosch, Apprich, Kneifel, & Novalin, 2013; Peila et al., 2016; Peila et al., 2016). Table 2 presents the effect of different treatments on donkey milk proteins.

The Holder Pasteurization (HoP) method (62.5–63 °C for 30 min) is an LTLT method and is the most extensively used as well as the recommended method by all international guidelines for the thermal processing of human donor milk (HMD) (Bertino et al., 2015; Peila et al., 2017;Peila, Coscia, et al., 2016; Peila, Moro, et al., 2016). HoP eliminates pathogenic viruses as well as bacteria; more specifically *Staphylococcus epdermidis, Escherichia coli, Staphylococcus aureus, Enterobacter cloacae* and *Bacillus cereus* are reduced by a 5-$\log_{10}$ (Christen, Lai, & Hartmann, 2012).

It is documented that nutritional properties as well as bioactive components are the main components that are negatively affected by HoP (Bertino et al., 2015; Peila, Coscia, et al., 2016). Most importantly, immunological components are the most affected components in human milk when is treated with the HoP method (Peila, Moro, et al., 2016); proteins with bioactive properties are substantially reduced. For example after HoP, only 39% and 22% of lysozyme and lactoferrin, respectively, were retained (Christen et al., 2012).

Immunoglobulins are used as qualitative parameters when comparing HoP method with other alternative methods because immunoglobulins (and other immunological components) are primarily affected by HoP (Peila, Coscia, et al., 2016; Peila, Moro, et al., 2016). Both HoP and HTST (72 °C for 15 s, 72 °C for 5 s and 71 °C for 9.0 s) showed equivalent reductions of immunoglobulin IgA (Dhar, Fichtali, Skura, Nakai, & Davidson, 1996; Goldsmith, Dickson, Barnhart, Toledo, & Eiten-Miller, 1983; Hamprecht et al., 2004); in contrast, a study reports no changes in IgA of human milk after HTST (72 °C for either 15 or 5 s) (Goldblum et al., 1984). In terms of the immunoglobulin IgG, HoP did not cause changes, whereas HTST (72 °C for 15 s and 71 °C for 9.0 s) resulted in a significant reduction (Dhar et al., 1996; Goldsmith et al., 1983). Both HoP and HTST significantly reduced IgM (Dhar et al., 1996; Goldsmith et al., 1983).

Regarding lactoferrin, both HoP and HTST treatments reduced its content in human milk. Peila, Coscia, et al. (2016) reports that lactoferrin in human milk was negatively affected more by HoP when compared to HTST. For lysozyme, the results vary between studies; a study reports that HoP does not affect lysozyme activity (Mayayo et al., 2016), while others report that both HoP and HTST reduce lysozyme levels by 35% and 20% respectively (Hamprecht et al., 2004). Both HTST (75 °C for 15 s) and HoP caused significant reduction of antioxidant activity, nonetheless, HoP caused higher reduction (Silvestre et al., 2008). Yvon et al. (2016) investigated the impact of heating on milk; non-heat treated donkey milk improved the Crohn disease ileitis damages compared to the heated donkey's milk which had no impact.

It is reported, as a conclusion, that HTST has, at least, the same ability as HoP in terms of providing microbiological safety of human milk. However, it is reported that HTST is superior in terms of having less impact on antioxidant potential of human milk as well as on the structure and content of lactoferrin and others like cytokines and Vitamins B and C (Peila et al., 2017). On the other hand, in terms of bactericidal capacity of human milk against *E.coli*, both HoP and HTST (75 °C for 15 s) causes reduction, however, HTST causes significantly higher reduction. It's reported that bactericidal capabilities of human milk are better preserved by HoP (LTLT) (Silvestre, Ruiz, Martinez-Costa, Plaza, & Lopez, 2008).

Regarding donkey milk, only recently a study by Giribaldi et al. (2017) demonstrated the effect of HTST on donkey milk. Results showed that HTST represents an interesting opportunity especially for small donkey's farms as it was able to reduce the total bacteria count, and to completely eradicate Enterobacteriaceae. Moreover it provides a better preservation of the protein fraction of raw donkey milk.

In order to preserve and also increase the donkey milk shelf life, some thermal treatments such as freeze-drying or spray-drying have already applied on donkey milk. All studies demonstrated that these treatments could affect the nutritional characteristics of donkey milk, even though more research is still needed (Polidori & Vincenzetti, 2013; Vincenzetti et al., 2011). For instance, in a study carried out by Vincenzetti et al. (2018) showed that both technological treatments (spray and freeze drying) affected β-lactoglobulin and lysozyme content in donkey milk, but did not have any effect on α-lactalbumin.

Therefore, according to the information above, thermal processing ensures food safety, but on the other hand there are detrimental effects on nutrients and bioactive compounds. As a result, research is directed towards alternative food processing methods (i.e. minimal processing) that ensure microbiological safety without negatively affecting organoleptic, nutritional characteristics and bioactive value (Ashenafi, 2012; Bansal, Siddiqui, & Rahman, 2014).

Several non-thermal processing methods have been studied for their impact on preserving bioactivity of human's milk; research indicates that there is a great potential on replacing the traditional holder pasteurization method with these new methods. Examples of this non-thermal processes includes high pressure processing, ultrasonic process and UV-C. These non-thermal processes have been recently reviewed (Peila et al., 2017).

Therefore, more research needs to be conducted to address whether processing of donkey's milk using different thermal and non-thermal processing techniques could result in deterioration of its bioactive and functional properties and nutritional quality. Such a product will be of interest not only for the infant's food industry but also to the pharmaceutical industry such as for the elderly and other immunocompromised groups of people.

9. Limitations

Despite the high and balanced essential fatty acid content, donkey's milk has a lower lipid content than human milk and other dairy animals and as a result it has lower calorific value (D'Auria et al., 2011). In a case study carried out by (D'Auria et al., 2011) It was demonstrated that the use of unmodified donkey's milk in a 5-month cow's milk-allergic infant can result to a nutritional imbalance which is characterised by low weight due to the lower caloric intake and also infant showed generalised hypotonia, abdominal distension, pallor and decreased muscle bulk. Another example of donkey milk allergy was described by Peeters et al. (2017). In this case a young woman with a history of personal atopic dermatitis, allergic asthma and hay fever, experienced a facial angioedema 5 min after consuming fresh donkey's milk. The development of this allergy could be partially explained by the fact that the patient was percutaneously sensitized through repeated contact of her atopic skin with donkey's milk-based emollients, and she subsequently developed immediate hypersensitivity reactions to donkey milk.

The donkey milk macro minerals concentration (Ca, P, K, Na and Mg) is similar to that of mare milk but on the other hand is lower than that of other ruminants. Nonetheless, donkey's milk macro minerals concentration is higher than that of human milk, hence infants can receive adequate amounts (Fantuz et al., 2012). Additionally, donkey's milk is characterised as a good source of zinc, iron and copper but is also rich in selenium; all these vary depending on the season and the geographical area (Potortì, Bella, Lo Turco, Rando, & Dugo, 2013). However, the case study showed that donkey milk was not only low in calories; it also caused iron deficiency anaemia due to its very low levels of iron. It also had very low levels of calcium (D'Auria et al., 2011).

. It is reported that the growth rate in the first year of life can affect the health of the person in its adulthood. The use of donkey milk, as a sole food in infant's diet, due to its low lipid and calorific value, cannot meet the dietary needs of the growing infant; hence it shouldn't be considered as an adequate source of calories to feed CMPA infants. It could however be used in infants diet only if is adequately supplemented (D'Auria et al., 2011).

Donkey's milk is believed to be suitable to be used in infant formulas in the first year of life (Bertino et al., 2010; Gastaldi et al., 2010). Clinical studies showed that this is well tolerated (82.6%–88%) by infants but it didn't achieve the minimum required 90% tolerability which will allow to characterise a donkey milk infant formula as hypoallergenic (American Academy of Pediatrics, 2000; D'Auria et al., 2011; Monti et al., 2007; Vita et al., 2007). Therefore, donkey's milk may not be suitable as a complete replacer of infant's formula, but it can act as a supplement to a balanced diet.

10. Conclusion

Due to its tolerability (i.e. digestibility, palatability, low allergenecity) and bioactivity (i.e. lysozyme activity), donkey milk could be used as a dietary supplement, in conjunction to a balanced diet, which will provide the bioactive and anti-infective components lacking from the conventional infant formulae. It could also be considered as a direct replacement of protein sources from infant's formula (i.e. extensively hydrolysed proteins or pure amino acids).

The calorific inadequacy, low lipid and iron contents of donkey milk must be covered by either fortification (i.e. with unsaturated fatty acids) or by consumption as part of a balanced diet.

Minimal processing of donkey's milk needs to be further evaluated as heat treatment has a negative impact on bioactive components.

Conflicts of interest

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