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Review

Recent advances in selective allergies to mammalian milk proteins not associated with Cow's Milk Proteins Allergy

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ABSTRACT

Cow's milk proteins allergy (CMA) is an atypical immune system response to cow's milk and dairy products. It's one of the most common food allergies in children affecting 8% of the total pediatric population pediatric population. This comprehensive review examines recent studies in CMA, especially regarding mammalian milk allergies such as goat's, sheep's, buffalo's, camel's, mare's and donkey's milk allergies in order to increase awareness of these selective allergies and to reduce allergy risks for those who have them. The consumption of other mammalian milk types is not recommended because of the significant homology between milk proteins from cow, sheep, goat and buffalo resulting in clinical cross-reactivity. However, camel's, mare's or donkey's milk may be tolerated by some allergic patients. Selective mammalian milk allergies are unusual and rare disorders characterized by severe symptoms including angio-oedema, urticaria, respiratory manifestations and anaphylaxis. Based on the reported allergic cases, cheese products including Ricotta, Romano, Pecorino and Mozzarella, are considered as the most common source of allergens especially in goat's, sheep's and buffalo's milk allergies, while the major allergens in donkey's and mare's milk seems to be whey proteins including lysozyme, α-lactalbumin and β-lactogloblin due to the low casein/whey proteins ratio in equine's milk.

1. Introduction

Cow's Milk Allergy (CMA) is a growing health concern worldwide, with a rising prevalence attributed to environmental and genetic factors. CMA is considered as the most common food allergy especially during childhood. It affects approximately 1–3% of adult population and 3–8% of pediatric population (Lajnaf et al., 2023; Liang et al., 2022; Moen et al., 2019). Furthermore, its confirmed that 2–6% of infants exhibit CMA in the first year of their life (Schouten et al., 2009). Indeed, in early life, children with food allergy show lower microbiota diversity and an altered fecal microbiota when compared to healthy controls (Lajnaf et al., 2023).

Recurrent and chronic adverse reactions to cow's milk are often classified into cow's milk allergy (CMA) or cow's milk intolerance (CMI). CMA and CMI are usually used synonymously or interchangeably by the public and health professionals. However, these two terms differ totally from each other linguistically and scientifically (Bahna, 2002). CMA is the main cause of serious and potentially fatal allergic reactions i.e. anaphylaxis in children. Indeed, this allergy is ranked third among all food allergies for the proportion of anaphylactic reactions ranging between 8 and 15% of cases (Cianferoni and Muraro, 2012; Lajnaf et al., 2023). Cow's milk is one of the main implicated foods on anaphylaxis whose incidence is three times higher in infants at the age below the age of 4, whereas, serious clinical manifestations were found to be frequent in patients over 5 years of age and with persistent CMA (Tejedor Alonso et al., 2012). Unlike other food allergies such as peanut allergy and sesame allergy, researchers noted that CMA is characterized by a high probability of tolerance after the age of 5 years (ranging between 80% and 90%) (Lajnaf et al., 2022a). Indeed, tolerance is a key player in holding allergic reactions down. It's defined as the process in which the immune system promotes systemic non-responsiveness to food antigens that are administered orally. Gut colonization and the diversity and

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intensity of microbial exposure can also play a crucial role in inducing cow's milk tolerance. (Vickery et al., 2011).

However, although the natural history of CMA usually shows a positive prognosis, with the majority of allergic children showing resolution during childhood, recent epidemiological studies suggest slower rates of resolution and higher rates of children with persistence of this immunological pathology into adolescence and even adulthood (D'Auria et al., 2018).

Serious symptoms pose a threat to the life of the allergic patient as they have been related to sudden death (Martorell-Aragonés et al., 2015). CMA is an IgE-mediated or non-IgE-mediated immune reaction, caused by milk proteins including both of whey proteins and caseins (D'Auria et al., 2018). Overall, 50% of the food-allergic population showed an IgE-mediated food allergy leading to various clinical manifestations including skin symptoms (70–75%), gastrointestinal symptoms (13–34%), respiratory problems (1–8%), different organs' alterations (26%), and finally severe anaphylaxic reactions (1–4%) (Martorell et al., 2006).

Most proteins in cow's milk, including the allergens, are glycoproteins (D'Auria et al., 2018; O'Riordan et al., 2014; Paschke and Besler, 2002). These proteins could be separated in two main fractions upon acidification at pH 4.6, ultracentrifugation or cheese coagulation using rennet enzyme (Liang and Luo, 2020). These fractions include the caseins and whey proteins. First, caseins, which are located in micellar complexes conferring its milky appearance, account for 80%, while whey proteins that represent the remaining 20% of the total bovine milk proteins (Lajnaf et al., 2023, 2022b; O'Riordan et al., 2014; Paschke and Besler, 2002). The group of caseins is characterized by Molecular Weights (MW) that range between 20 and 30 kDa, it includes α_{S1}- (12–15 g/L), α_{S2}- (3–4 g/L), β- (9–11 g/L), κ- (6–8 g/L) and γ- (3–4 g/L) caseins. On the other hand, whey proteins comprise β-lactoglobulin (3–4 g/L; MW 18.3 kDa), α-lactalbumin (1–1.5 g/L; MW 14.2 kDa), bovine serum albumin (0.1–0.4 g/L; MW 67 kDa); immunoglobulins (0.6–1 g/L; MW 160 kDa) and lactoferrin (0.09 g/L; MW 76–80 kDa) (Besler et al., 2002; Wal, 1998). Currently, the diagnostic work-up of CMA allergy is based first on a medical interview followed by detailed clinical and physical examination and finally by both of *in vitro* or *in vivo* tests to detect immunoreactivity against specific allergens (Fiocchi et al., 2010). Cow's milk contains various proteins. Only some of these proteins are reported to be allergenic. Indeed, the proteins most frequently recognized by specific IgE in cow's milk are caseins (also called Bos d8) includeing the following known isoforms: α_{S1}-casein (Bos d9), α_{S2}-casein (Bos d10), β-casein (Bos d11) and κ-casein (Bos d 12). Furthermore, whey proteins appear to be potential allergens even those that are present and low amounts such as lactoferrin, BSA, immunoglobulins. These minor proteins were not detected by convential *in vitro* tests, probably due to its low concentration that makes it obscured by the strong signals of more abundant immune-reactive proteins in the sample. Allergens in the soluble fraction of cow's milk consist of β-lactoglobulin (Bos d 5), α-lactalbumin (Bos d 4), BSA (Bos d6), immunoglobulins (Bos d7), and lactoferrin (Bos d lactoferrin) (D'Auria et al., 2018).

Caseins are generally considered as the main allergen in milk especially α_{S1}-casein. Previous authors reported that the high allergenicity of caseins is associated to its high content in cow's milk (30 g/L) and to its higher thermostability when compared to whey proteins (Xu et al., 2016). Other studies noted that the β-lactoglobulin (Bos d5) is considered as the most important allergen in cow's milk especially for allergic children. Indeed, this protein is reported to be responsible for 60–80% of total allergic reactions in CMA patients, probably to the absence of this protein in human's milk (Stöger and Wüthrich, 1993). Other researchers reported that the β-lactoglobulin and caseins are the main allergens in cow's milk representing 66% and 57% respectively of milk allergy cases, followed by both of α-lactalbumin and BSA representing together 18% of total cases (Miciński et al., 2013; Peñas et al., 2006). Hochwallner et al. (2014) confirmed that caseins are the most potent allergens which an allergenic activity that ranges between 35% of patients (β-casein) and 26% (both of α_{S1}-casein and κ-casein) (Hochwallner et al., 2014). For the whey fraction, the highest allergenic activity was attributed to β-lactoglobulin (19%) followed by α-lactalbumin (12%) and BSA (1%) (D'Auria et al., 2018; Hochwallner et al., 2014).

IgG (Bos d7) was reported as potential milk allergen due to the observation of specific IgE from milk allergic patients specifically towards bovine IgG. Furthermore, approximately 10% of patients with CMA allergy are IgE-positive to bovine IgG, this protein is considered as a minor allergen in milk (Villa et al., 2018). On the other hand, Some studies declare that some milk-allergic individuals possess lactoferrin-specific IgE. In the same way, the allergenicity of lactoferrin (Bos d lactoferrin) was explored using mouse model of allergy by measuring anti-lactoferrin antibodies responses and *in vivo* anaphylactic reactions in lactoferrin sensitized mice (Negaoui et al., 2016). This work confirmed lactoferrin exhibits a strong allergenicity. Indeed, all mouse groups developed important clinical symptoms of anaphylactic reactions at different stages (Negaoui et al., 2016; Zhou et al., 2014).

In recent years, there has been a significant rise in the number of patients with CMA of all ages. Consequently, scientists are influenced towards frequently choosing hypoallergenic formulas as alternatives to cow's milk, including milk other mammalian species. However, these formulas can not only present cross reaction risks but also induce alone a specific allergy that is not associated with that of cow's milk. These allergies are unusual and rare and have been previously reported only as case reports (Lajnaf et al., 2023; Pham and Wang, 2017).

Up to now, there is no review available for mammalian milk allergies including goat's, sheep's, mare's, donekey's, buffalo's and camel's milk allergies. Thus, in the present review, we sought to summarise the different recent investigations including the different cases reports mammalian milk allergies which are not associated with CMA. This study covers the nutritional composition, the cross reactions to CMA patients, their ability to replace milk for patients with CMI, as well as the selective allergy of these milks as seen by various authors.

2. Mammalian milk in CMA and CMI

2.1. Nutritional composition and cross-reactivity of mammalian milk proteins in CMA

The nutritional composition of milk varies greatly from species to other species as reviewed by different authors depending on to their phylogenetic pathways (Alston-Mills, 1995; Bittante et al., 2021; Faccia et al., 2020; Maryniak et al., 2022; Nayak et al., 2020).

Overall, the main component in milk is water with a percentage ranging between 84% and 90.6% depending on animal species, genetic factors, physiological factors, nutritional factors and environmental conditions. The water content in donkey's milk is the highest followed by mare's, camel's, cow's, goat's, buffalo's and sheep's (Nayak et al., 2020).

First, the overall nutritional composition of the human milk is comparable to mare and donkey milk, as it contains similar basic chemical compositions compared to other animal milk composition (Nayak et al., 2020). First, the fat contents vary considerably depending on mammalian milk alternative. These milk alternatives (goat's, sheep's, mare's, denkeys, buffalo's and camel's milk) vary in their composition of both of macro and micronutrients. In terms of macronutrients, one can distinguish milk rich in proteins, fats, and lactose, such as Caprinae subfamily (goat's and sheep's milk), from those characterized by a low protein, fat and high lactose content, such as donkey's and mare's) (Table 1). First, sheep's milk has the highest fat content compared to other mammalian milk, followed by buffalo's, cow's, camel's, goat's, mare's and donkey's milk, while equine's milk contains lower amount of fat contents compared to other milk sources leading to the lowest energetic level compared to other milk sources (Nayak et al., 2020; Verduci et al., 2019). The highest mineral contents were found also to be highest in buffalo's and sheep's milk followed by cow's, goat's

Table 1
Nutritional composition (g/100g) of different types of milk of animal origin: cow's, buffalo's, sheep's, goat's, mare's, donkey's, human's and camel's milk (Nayak et al., 2020; Sabahelkhier et al., 2012).

	Cow	Buffalo	Goat	Sheep	Donkey	Mare	Camel	Human
Energy (kcal)	64	102.3	64	89.8	40	48	61	70
Water	87.8	82.7	87.7	81.6	90.7	89.8	88	87.5
Total protein	3.2	5	3.2	5.7	1.9	2,1	3	1.0
Total fat	3.6	7.1	3.6	7.3	0.8	1.2	3.6	4.4
Lactose	4.7	4.6	4.7	4.6	6.3	6.4	4.3	6.9
Ash	0.7	0.9	0.7	0.8	0.4	0.4	0.7	0.2

and camel's milk (0.7%). The ash contents were the lowest for human's milk (0.2%) and equine's milk (0.4%) (Table 1). The highest lactose contents were observed in human milk (6.8%, w/v) followed by mare and donkey milk (~6.3%, w/v) compared to cow's, goat's, sheep's, camel's and buffalo's milk. The high content of lactose in milk is responsible for the good palatability and facilitates the intestinal absorption of calcium to infants. The protein contents in sheep's and buffalo's milk are the highest protein contents (>5%, w/v) among all mammalian species including human's, cow's, goat's, camel's, mare's and donkey's milk (Nayak et al., 2020; Sabahelkhier et al., 2012).

The casein and whey protein combination of human milk is similar to donkey's and mare's milk compared to cow's, buffalo's, goat's, sheep's and camel's milk. An average, equine's milk contains a low level of total protein as well as a low casein/whey protein ratio (average of 1.3), followed by camel milk (ratio raging between 52 and 87%) as reported by previous authors (Bittante et al., 2021; Nayak et al., 2020; Tidona et al., 2011).

Human's milk is characterized by the lowest proteins contents among all mammalian species (1%, w/v), leading to avoid an excessive renal load of solute. Furthermore, human's milk showed the lowest casein/whey protein ratio. Indeed, only 26% of total human's milk proteins are caseins, while caseins represent approximately 80% of bovine proteins (Nayak et al., 2020). Human's milk is distinguished from other mammalian milk by a specific proteins composition. Indeed, this milk contains the lowest amounts of α_{S1}-casein (0.3–0.8 g/L) (Bos d9) among all mammalian milk with a high concentration of β-casein (1.8–4 g/L) (Bos d11). It is also deficient in both of α_{S2}-casein (Bos d10) and β-lactoglobulin (Bos d5) (Table 2). Both of donkey's and mare's milk have the most comparable protein composition with human milk including the low content of casein and the lack of α_{S1}-casein protein (Table 2). Donkey's and mare's milk present high amouns of β-casein that ranges between 3.9 and 11 g/L in both milk, and high concentrations of β-lactoglobulin (higher than 3 g/L) and α-lactalbumin (ranging between 1.8 and 3.3 g/L) (Table 2). Camel's milk also has valuable nutritional properties as it contains a high concentrations of antibacterial substances and 5 times higher concentration of vitamin C compared to cow's milk (Al Kanhal, 2010; Farah et al., 1992). Camel's milk is characterized by a particular protein composition such as the dominance of β-casein (15 g/L) and deficiency of β-lactoglobulin (Bos d5) similarly to human's milk (Table 2) (Lajnaf et al., 2021, 2022b). On the other hand, cow's, sheep's and buffalo's milk, regarding the high content of protein including caseins and also fats make a very good raw material for processing, especially cheesemaking (Bittante et al., 2021). Cow's, buffalo's, sheep's and goat's milk showed high levels of individual caseins especially α_{S1}-casein and β-casein (Table 2). On the other hand, a low casein/whey protein ratio in equine's and camel's milk is reported to reduce the its allergenic capacity (Lara-Villoslada et al., 2005; Nayak et al., 2020).

Despite their nutritional interest, mammalian milk present potential risks for the health of patients with CMA because of the high cross-reactivity with bovine milk proteins. Cross-reactivity in allergic reactions is defined as the same immune response for two antigens because of a similar antigenic determinant. Cow, goat, sheep, and camel belong to the order Artiodactyla. The order Artiodactyla is divided into two suborders: Ruminantia and Tylopoda suborders. Ruminantia suborder includes cow (Bovidae family) as well as goat and sheep (Caprinae family). Meanwhile, Tylopoda suborder includes camel which belongs to Camelidae family. Horse and donkey belong to another order called Perissodactyla and further belong to the same suborder Hippomorphia, family Equidae, subfamily Equinae, and genus Equus, and hence, they differ only in their species (Maryniak et al., 2022).

Cow, sheep and goat are phylogenically related animals, high homology exists among their milk proteins (over 82% of identity level) (Table 3). Indeed, sheep and goat are in the same subfamily and are more closely related to each other than to cow and buffalo. Patients with CMA often have allergic reactions triggered by ingestion of both of goat's and sheep's milk. In prior studies, approximately 92% of patients with CMA reacted to goat's milk which is attributed to the high homology between caprine and bovine proteins ranging between 82.4% (κ-casein, Bos d12) and 96.3% (β-lactoglobulin, Bos d5). Hence, a high homology level between caprine and bovine proteins that ranges between 82.4 and 96.3% leads to a significant risk of cross-reaction (over 92% of patients with CMA).

On the other hand, donkey and horse belong to another order called Perissodactyla and further belong to the same suborder (Hippomorphia), family (Equidae), subfamily (Equinae), and genus (Equus) and differ only in their species. Different protein composition was reported such as low contents of α-casein leading to low cross reactivity risk between equine and bovine proteins. That small number of people with CMA have tried to consume milk from buffalo and donkey with some safe successful *in vivo* and *in vitro* trials to donkey and mares milk, Indeed, only 8% and 4% of patients with CMA reacted to donkey's and mare's milk, respectively due to the lowest identity level between equine and bovine proteins (below 51% for caseins, Bos d8). Hence, preleminary studies showed that a low homology level between mare's and cow's milk proteins that ranges between 38.2% (α_{S1}-casein, Bos d9)

Table 2
Comparison of the concentrations (g/L) of the main proteins of in different mammalian milk (Kappeler, 1998; Roy et al., 2020; Wal, 1998).

Protein	Cow	Buffalo	Goat	Sheep	Donkey	Mare	Camel	Human
Caseins								
α_{S1}-casein	10.0–15.0	8.9	0–7.0	3.0–6.0	0.2–2.0	2.5	5.0	0.3–0.8
α_{S2}- casein	3.0–4.0	5.1	4.2	9.0–12.0	0.2	0.2	2.2	–
β- casein	9.0–11.0	12.6–20.9	11.0–18.0	19.0–28.0	3.9	11.0	15.0	1.8–4.0
κ- casein	3.0–4.0	4.1–5.4	4.0–4.6	4.0–5.0	–	4.6	0.8	0.6–1.0
Whey proteins								
β-lactoglobulin	3.0–4.0	3.9	2.1	5.6–7.2	3.2–3.7	3.0	–	–
α-lactalbumin	1.0–1.5	1.4	1.2	1.7	1.8–3.0	3.3	3.5	1.6

Table 3
Comparison of Amino Acid sequence identity (%) of milk proteins from different mammalian Species (Gu et al., 2023; Lajnaf et al., 2022b, 2023).

Protein	Cow	Buffalo	Goat	Sheep	Donkey	Mare	Camel	Human
Caseins								
α_{S1}-casein	100%	95.3%	86.9%	87.4%	39.0%	38.2%	44.6%	26.6%
α_{S2}-casein	100%	89.6%	87.5%	88.0%	56.1%	53.1%	58.3%	–
β-casein	100%	97.8%	90.9%	91.4%	53.1%	53.1%	67.2%	49.3%
κ-casein	100%	92.6%	82.4%	82.5%	51.8%	51.4%	58.4%	49.4%
Whey proteins								
β-lactoglobulin	100%	98.6%	96.3%	95.7%	56.2%	57.4%	–	–
α-lactalbumin	100%	96.1%	94.3%	96.7%	71.5%	72.4%	69.1%	75.6%

and 72.4% (α-lactalbumin, Bos d4) leads to a low risk of cross-reaction (only 4% of patients with CMA). In the same way, the homology between cow's and donkey's milk protein are reported to be lower especially when compared to goat's, sheep's and buffalo's milk, ranging between 39% (α_{S1}-casein, Bos d9) and 71.5% (α-lactalbumin, Bos d4). These levels of homology are in great consistence with the low corss reactivity between donkey's and cow's milk.

However, these trials are limited to confirm this milk as suitable alternative for children with CMA and further studies are needed to consider donkey's milk as an hypoallergenic formula in CMA. Furthermore, donkey's milk showed a calorific inadequacy including low lipid and iron contents that should be covered by either fortification (i.e. with unsaturated fatty acids) or by consumption as part of a balanced diet (Souroullas et al., 2018). On the other hand, high cross reactivity was observed with milk proteins from buffalo milk, while none of anti-cow milk proteins antibodies reacted with proteins from camel's milk proteins due to the absence of the β-lactoglobulin in camel milk (Table 2) (El-Agamy et al., 2009; Restani et al., 2002). Consequently, equine's and camelid's milk are considered as promising alternative proteins sources for patients with CMA due to low sequence identity levels to bovine proteins leading to weak cross-reaction as confirmed by various *in vivo* and *in vitro* studies. However, further nutritional studies are required to confirm the calorific adequacy of these milk especially to pediatric population.

2.2. Mammalian milk and CMI

Unlike CMA, CMI results from a reduced capacity to digest lactose in cow's milk by Lactase enzyme (β-galactosidase) and not synonymous with hypersensitivity. It causes symptoms only in the bowel including abdominal pain, bloating, flatus, and diarrhea (Walsh et al., 2016). Primary CMI develops when levels of the enzyme lactase reduce usually after 3 years of age in some populations (Africans and Asians). Meanwhile, secondary CMI is induced by mucosal damage and usually following coeliac disease and CMA. It is usually reversible once the epithelial lining has repaired. Except after a gastrointestinal infection, infants with gastrointestinal symptoms on exposure to cow's milk are more likely to have cow's milk allergy than lactose intolerance (Walsh et al., 2016). The major treatment of CMI is avoidance of food containing any amount of lactose, whereas people who avoid milk for an extensive period of time have a loss of production of the enzyme that breaks down the disaccharide and would prevent the response. Indeed, lactose is the only carbohydrate of mammalian milk and it is not present in any other food. Its quantity is highest in human milk (6.9 g/100g) followed by equine's milk (6.3–6.4 g/l00g). Furthermore, there are minor differences in the lactose content between cow's, buffalo's, goat's, sheep's and camel's milk according to Table 1.

Even where there is a strong family history, it is extremely rare for an infant to be born with primary lactose intolerance. Lactose intolerance rarely develops before the age of 4 years. On the other hand, secondary lactose, a temporary condition following a bout of diarrhea, can occur in infancy. Despite its high contents in lactose, Human's milk has healing properties that will assist an infant's gastrointestinal tract to recover faster and should be encouraged. Lactose overload (functional lactase deficiency), which is a relatively common condition for breastfed infants in the early weeks and months, is often misdiagnosed as lactose intolerance. Breastfeeding should be continued as gastric symptoms can be reduced with simple feeding management (Koura, 2019).

The use of mammalian milk in the prevention of lactose intolerance in patients with CMI seems controversial, with studies showing some prophylactic effect of mammalian milk when compared to cow's milk, whereas other studies did not show such effect. For instance, goat's and sheep's milk products appear to become suitable as a substitute for people (including children) suffering from CMI (Ballabio et al., 2011).

Individuals with lactose intolerance can consume dairy products with low lactose content. Available data suggest that both of adults and adolescents with diagnosis of lactose intolerance could ingest at least 12 g of lactose in a single dose without or with minor symptoms. However, previous works highlight that the digestive discomfort of milk intolerance is complex and it is impacted by more than just lactose in milk (Shrestha et al., 2021). For instance, Cardoso et al. (2010) noted that the use of camel's milk could contribute to the reduction of gastrointestinal disorders that occur in patients intolerant to lactose leading to suggest it as an alternative to cow's milk for individuals with CMI despite the high lactose contents in this milk (4.3% w/v). Indeed, this behavior was explained by the fact that camel's milk is more easily metabolized than other mammalian of milk. Furthermore, it produces less casomorphines than bovine milk, which would provoke less intestinal motility and would lead lactose to become more exposed to the action of lactase. Meanwhile, Health Organization recommend human's milk consumption for infants, despite the high lactose content of milk with the improvement of symptoms and the lactase enzyme activity when compared with infants who received infant formula (del Carmen Tocaa et al., 2022). For equine's milk, there are no specific studies regarding the use of donkey's milk in subjects with lactose intolerance. Lactose-free DM is currently not available on the market. However, authors suggest that this milk seems inadequate for people suffering from lactose intolerance as it presents high lactose content compared with other ruminant milk (Madhusudan et al., 2017). Further studies are needed to confirm mammalian milk as suitable alternatives for people suffering from CMI.

3. Selective mammalian milk allergies

Mammalian milk proteins including goat's, sheep's, buffalo's, mare's, donkey's and camel's milk are found to be able to induce rare and unusual allergies which is not associated with that of cow's milk. Unlike CMA, selective allergies to mammalian's milk without concomitant CMA have been reported as case reports (Pham and Wang, 2017).

3.1. Goat's milk allergy

Goat's milk allergy not associated with CMA is defined as a rare disorder nutritional pathology which was first described by Wuthrich and Johansson in 1995 (Tavares et al., 2007). Caseins are considered as the major allergen inducing symptoms for goat's milk allergy including α_{S1}-, α_{S2}- and β-caseins as IgE antibodies of goat's milk allergic patients recognized principally caseins (Tavares et al., 2007). However, allergens other than caseins can be involved in allergy to goat's milk including α-lactalbumin (Järvinen and Chatchatee, 2009; Tavares et al., 2007). This selective allergy affects patients who are mostly older than those who with CMA with a mean age of 6 years and with a multiple food allergies (to at least to 3 foods) (Ah-Leung et al., 2006). The prevalence of goat and sheep milk allergy was 26% in a community of cow's milk allergic children which are treated with oral immunotherapy (n = 58) (Rodriguez del Rio et al., 2012). The symptoms are generally severe with various cases of angio-oedema or anaphylaxis induced by the ingestion of small amounts of goat's milk or cheese (Ah-Leung et al., 2006; Bidat, 2010). In the same way, Tavares et al. (2007) described a 27-year-old female who tolerated cow's milk and sheep's milk but suffered from persistent asthma and rhinitis since the age of 20 years and experienced two episodes od urticaria. Skin prick tests which were performed with caprine milk and cheese as well as bovine milk, caseins and α-lactalbumin, yielded positive reactions to goat's milk and cheese and negative reactions to cow's milk and dairy products. Indeed, the lack of clinical cross-reactivity of goat's and sheep's milk allergic patients to bovine milk products was attributed to the exclusive recognition of anti goat's milk IgEs to goat's and sheep's milk proteins and not to the absence of binding to cow's milk allergenic epitopes (Vereda et al., 2006). However, *in vitro* immunoblotting tests showed that the α-lactalbumin is also an allergen which is responsible for the sensitization in goat's milk allergy patients (Tavares et al., 2007). On the other hand, four allergic children to goat's and sheep's milk allergy and with no concomitant CMA were reported in Spain (Vereda et al., 2006). The analysis of Specific IgE antibody concentrations to cow's, goat's and sheep's revealed a high levels of IgE for goat's milk (47.71 kU/L) and sheep's milk (47.99kU/L). However, a very low IgE levels for cow's milk were found (1.27 kU/L) (Vereda et al., 2006).

3.2. *Sheep's milk allergy*

Sheep's milk is able to cause a selective allergy that is not associated with that of cow's milk. This allergy is a rare clinical condition and is mainly reported from countries with a higher consumption of ovine milk products (Rodriguez del Rio et al., 2012). Sheep's milk allergy induces severe reactions caused by anaphylactic shock leading to death (Pham and Wang, 2017). For instance, sheep's cheeses are well known by their ability to induce alone this unusual allergy which through few cases that have been detected in the world. First, one case report described a two children with the age of 10 years and 15 years in USA who had sheep's milk allergy and had experienced anaphylactic reactions to two types of sheep's milk cheeses: Ricotta and Romano (Table 4). The first subject (10 year-old boy) tolerates cow's milk products as it didn't show a concomitant CMA, while the second subject (15 year-old boy) had a long history of severe allergy to cow's milk proteins. For the first subject, IgE-ELISA was undetectable for bovine milk (<0.35 kU/L) and positive for ovine milk (~29.2 kU/L). However, IgE-ELISA was significantly high including both of sheep's (~48.9 kU/L) and cow's (~34.1 kU/L) milk for the second subject (Pazheri et al., 2014). The first subject could consume bovine dairy products without cross-reactivity between cow's and sheep's milk contrary to the second subject. Similarly, van Gemert and Gerth van Wijk (2021) described a 26-year-old woman with moderately severe atopic dermatitis and asthma and who showed her first occurrence of allergic symptoms at 21 years of age. This patient had no allergic symptoms on consumption of cow's milk or bovine dairy products including yogurt and cheese. However, she had anaphylaxis after ingestion of cheese as she used to handle pecorino cheese which is made from sheep's milk dring her work. These authors reported that this patient who had positive skin test reactions and specific IgE levels to sheep's milk, sheep's milk yogurt and pecorino cheese also had IgE antibody bound to the α_{S2}-casein in sheep's milk and not to that in bovine milk (van Gemert and Gerth van Wijk, 2021).

Table 4
Cases presentation of specific allergies to mammalian milk: sample population, symptoms and experimental results.

Mammalian milk allergy	Sample population	Symptoms	Results and conclusion	References
Goat's milk allergy	A 27 years-old female patient suffering from asthma and rhinitis since 20 years of age and showing allergic symptoms to caprine milk and cheese She tolerated cow's milk dairy products and sheep's cheese.	Symptoms started at 24 years of age with two episodes of urticaria after ingestion of goat's cheese (after 2 h after intake of caprine cheese).	Positive *in vivo* skin tests reaction to goat's milk and cheese and negative to cow's milk proteins (casein and α-lactalbumin). The appearance of IgE-binding 14 kDa band within *in vitro* immunoblot analysis totally inhibited after serum pre-incubation with goat's milk. Caseins and partly α-lactalbumin: the allergens most frequently responsible for allergic reactions in goat's milk allergy.	Tavares et al. (2007)
Sheep's milk allergy	Two children of sheep's milk allergy: – Subject 1: A 10-year-old boy: allergic to sheep's cheeses –Subject 2: A 15- year-old boy with a concomitant allergy to cow's milk	Anaphylactic reactions to two sheep's milk cheeses: Romano and Ricotta cheeses (subject 1).	–Subject 1: Positive IgE-ELISA results for sheep's milk (~29.2 kU/L) and negative results for cow's milk (<0.35 kU/L): –Subject 2: high IgE-ELISA levels for both of sheep's milk and cow's milk (ranging between 34.1 kU/L and 48.9 kU/L).	Pazheri et al. (2014)
	A 25-year-old woman with severe asthma and atopic dermatitis	First anaphylactic episode at 21 years of age associated with, laryngeal swelling, hand numbness vomiting and diarrhea Second anaphylactic episode at age 23 years, associated with facial oedema, vomiting, sneezing and rhinorrhea, and after eating sheep's cheese: Picorino.	–Positive skin test reaction to Picorino cheese and negative reactions to Camembert and Parmesan cheeses. –2-dimensional electrophoresis and immunoblotting reveiled that the main allergen in sheep's milk is the α_{S2}-casein. –High specific IgEs level of sheep's milk and whey and negative results of cow's milk proteins (caseins, α-lactalbumin and β-lactoglobulin).	van Gemert and Gerth van Wijk (2021)

(*continued on next page*)

Table 4 (*continued*)

Mammalian milk allergy	Sample population	Symptoms	Results and conclusion	References
	Subject 1: a 13-year-old girl Subject 2: a 34-year-old woman	Anaphylactic reaction with dyspnea, tightness, and nausea but without vomiting (subject 1) Allergic reaction with angioderma (subject 2)	−Positive skin prick test result for buffalo's mozzarella (subject 1) −Positive skin prick test reaction for cow's and buffalo's milk (subject 2)	Herz and Kopp (2020)
Donkey's milk allergy	−Subject 1: a 9-year-old girl with previous anaphylactic reactions to tree nuts and peanuts −Subject 2: a 33-year-old woman with no CMA	Generalized urticaria after an application of a cream containing donkey's milk (Suject 1) Angioedema symptoms associated with general discomfort, sweating and xerostomia after testing donkey's milk drops (subject 2)	−Positive skin test results to donkey's milk and negative reaction to bovine milk, caprine milk and ovine yogurt (Subject 1) −Positive skin test reaction to donkey's milk and donkey's milk based creams (Subject 2) −Specific IgE to donkey's lysozyme (Subject 1 and 2)	Martini et al. (2018)
Mare's milk allergy	A 45-year-old woman with no concomitant CMA.	Rapid swelling of the eyelids and itchy wheals on the face after the application of a cosmetic cream containing mare's milk proteins	Positive specific IgEs results for mare's milk (>100 kU/L) and mare's milk α-lactalbumin (77 kU/L).	Verhulst et al. (2016).
	A 51-year-old woman with no concomitant CMA	Severe anaphylactic reaction requiring emergency: severe hypotension, angioedema and allergic asthma	−Strong positive skin test reaction to mare's milk and negative reaction to bovine milk −Reduction of the whey proteins allergenicity (α-lactalbumin and β-lactoglobulin) after heating treatment at 92 °C–97 °C during 30 min	Gall et al. (1996)
Camel's milk allergy	Nine allergic patients with a mean age of 4.3 years (four male patients and five female patients) with a history of food allergies	Anaphylaxis (four patients) and cutaneous urticaria and/or angioedema (five patients)	−High IgE levels and blood eosinophil counts. −Positive skin test responses for camel's milk.	Ehlayel and Bener (2018)

3.3. Buffalo's milk allergy

Despite the high level of homology with cow's milk, buffalo's milk allergy is poorly investigated and only few cases were previously described (Table 4). Recently, two allergic cases to buffalo's milk were investigated. The first case report described a 13-year-old girl in Germany who had an anaphylactic reactions after ingestion of buffalo mozzarella and had positive test reactions to buffalo's cheese, whereas she tolerated cow's milk proteins. On the other hand, a second allergic case study reported a 34-year-old woman who showed an allergic reaction to the buffalo's mozzarella with positive skin test reaction both of buffalo's and cow's milk (Herz and Kopp, 2020).

3.4. Donkey's milk allergy

As observed for goat's, sheep's milk and buffalo's milk, Equine's milk induces a selective allergy which is not associated with CMA. Thus, donkey's milk proteins allergy is rare nutritional pathology which was recently investigated (Souroullas et al., 2018). Martini et al. (2018) described two cases of allergy to donkey's milk in Italy, a first 9-year-old girl previous anaphylactic reactions to peanut tree nuts and who showed a generalized urticaria after an application of a cream containing donkey's, and a second 33-year-old woman with no CMA and who presented an angioedema within a few minutes after tasting donkey's milk drops. Skin tests were positive with donkey's milk and negative with goat's milk and sheep's yogurt. These authors confirmed that lysozyme protein in donkey's milk is responsible for this selective allergy and for the potential cross-reactivity with mare's milk (Ryskaliyeva et al., 2018).

3.5. Mare's milk allergy

Although mare's milk allergy seems to be rare, a few cases of anaphylactic reactions and/or protein contact dermatitis have been previously reported in the literature (Table 4). Indeed, mare's milk proteins especially whey proteins including α-lactalbumin and β-lactoglobulin were reported to be able to induce a selective mammalian allergy which is not associated with CMA (Gall et al., 1996). One case report described 45-year-old Caucasian women who showed itchiness and swelling on the face after application of a body cream containing mare's milk proteins as an ingredient. Measurement of specific IgE in the patient's serum revealed positive results to mare's milk (>100 kU/L) and α-lactalbumin (77 kU/L) (Verhulst et al., 2016). On the other hand, Gall et al. (1996) descrived a case of anaphylactic reaction to mare's milk in a 51-year-old woman who was allergic to α-lactalbumin and β-lactoglobulin in mare's milk and she was able to tolerate cow's milk. These authors evidenced the existence of an IgE-mediated mare's milk allergy which was caused by mare's whey proteins (α-lactalbumin and β-lactoglobulin). However, these proteins were reported to disappear after heating treatment at 92 °C–97 °C during 30 min. Furthermore, these proteins do not cross-react with their counterparts in cow's milk.

3.6. Camel's milk allergy

Despite its nutritional value and its particular protein composition leading to a low cross reactivity to cow's milk proteins, camel's milk proteins are able to induce sensitization as milk from other mammalian species including ruminants and equines (Table 4). Camel's milk allergy has been reported to be a very rare disease entity with systemic and cutaneous allergic reactions. Nine camel's milk allergic patients (with the mean age of 4.3 years) who had a family history of allergies were reported by Ehlayel and Bener (2018). These patients showed different symptoms such as cutaneous urticaria and angioedema (55.6%) and anaphylaxis (44.4%) and showed high specific IgE levels and blood eosinophil counts. As expected, positive cutaneous test with camel's milk were reported for all camel's milk allergic patients which was explained by the high contents of β-casein in camel milk (Ehlayel and

Bener, 2018). Camel's milk allergy is a distinct nutritional pathology which is usually concomitant other allergies such as CMA. Risk factors are atopic dermatitis, positive family history, and early life exposure to camel's milk (Ehlayel and Bener, 2018).

4. Management of mammalian milk allergies

According to the latest statistics of Food and Agriculture Organization (FAOSTAT, 2021), goat's milk and sheep's milk account for approximately 2,26% and 1,14%, respectively, of the total milk production in the world, after cow's milk (81.26%) and buffalo's milk (15%) (FAOSTAT, 2021). The equine's milk production is the lowest among all mammalian species with an average less than 0.1% of total milk production (Lajnaf et al., 2023). It is expected that production and consumption of the other mammalian milk will continue to increase significantly worldwide. More cases of selective mammalian milk allergy could be encountered in the future. Furthermore, it is obvious that these allergies are considered as unusual and rare of which only few cases have been reported contrary to CMA, whereas, these allergies are characterized by severe symptoms that can be elicited even after the ingestion of small quantities of mammalian milk and products. In the same way, death in the case of sheep's milk allergy has been previously reported (Ah-Leung et al., 2006).

Food labeling is a major management tool in the world. Thus, guidelines in Tunisia requires products to declare the 8 major allergens including milk and dairy products, cereals containing gluten, eggs and products thereof, crustaceans, fish, peanuts and soybeans, nuts and products thereof and sulphites with a concentration of 10 mg/kg or more. The presence in any food or food ingredient obtained using biotechnology of an allergen transferred from any of these food products shall be declared. Where it is not possible to provide, through labeling, the appropriate information regarding the presence of an allergen, the food containing the allergen must not be marketed (USDA Tunisia, 2019). However, other mammalian milk products that are not governed by these laws as Tunisian guidelines of allergens unfortunately covers only cow's milk. It should include also other allergens such as sheep and goat's milk, possibly buffalo. Consequently, there is little guidance from labeling for other mammalian milks to allergic patients. Indeed, Tunisian Law requires that the labeling of foodstuffs includes, in Arabic, the mandatory particulars: the list and the quantity of food ingredients. Hence, for any mammalian milk allergic patient should check and read the food label using the allergen's common name. For specific mammalian milk allergies, cheese products, which are composed of casein proteins, are the most common source of allergen cross-contamination especially goat's, sheep's and buffalo's cheeses (Pecorino, Ricotta, Romano and Mozzarella). Furthermore, goat's, sheep's and camel's milk are used in the same way as bovine milk and can be processes into evaporated milk, dried milk and dairy products such as yogurt.

Overall, management of food allergy consists of educating patients to avoid potential allergens and teaching them to initiate treatments of allergic reactions due to accidental ingestions. Eating out with CMA and/or selective mammalian milk allergy in restaurants or at friends' homes may become difficult, which may impact the socialization of the individual. Hence, it should be carried out with considerable caution. Indeed, restaurants usually use milk preparations and cheeses which were manufactured by mammalian milk proteins, making risk of cross-reactivity and/or cross-contamination. Cross-reactivity was detected for milk proteins from goat's and sheep's with buffalo's and camel's milk proteins (De Luca et al., 2022). A careful selection of low-risk restaurants is key for minimizing the chances of an allergic reaction especially through cross-contamination. Avoiding desserts, sauces, fried foods, and foods in covered pastry will help minimize the chance of an accidental ingestion of an allergen. Overall, a large majority of accidental ingestion leading to anaphylactic reactions occur generally outside the home at restaurants and social gatherings. Hence, buffets are best avoided as they offer a tremendous risk for cross-contact with allergens (Muñoz-Furlong and Sampson, 2008). Furthermore, restaurant chef and agents should be informed in order to avoid any risk of allergic reactions caused by mammalian milk products and ingredients (Pham and Wang, 2017).

Previous researchers reported that reducing the allergenicity of food materials using food processing has recently become an increasingly attractive tool for preventing food allergies especially heating processes (Pi et al., 2022). For instance, it is previously reported that the majority of children with milk allergy tolerate heated milk (75%) when it is processed at 260 °C during 3 min in muffin and waffle products contained 1.3 g milk protein (nonfat dry milk powder) (Nowak-Wegrzyn et al., 2008). On the other hand, 56% of children with CMA tolerated cake products containing milk, with the only condition that it was baked at 180 °C for at least 30 min (Sopo et al., 2016). Thus, heating process was reported to decrease the immunoreactivity of bovine milk leading to a safe consumption of extensively heated cow's milk by children with CMA (Maryniak et al., 2022). However, heating appeared to have increased immunogenicity of goat's and sheep's milk (Bencharitiwong et al., 2013). Avoidance of both of goat's and sheep's milk in all forms is recommended given these limited data suggesting increased allergencity upon heating (Pham and Wang, 2017).

Allergic patient are also advised to be aware of food items that might have as a minor or hidden ingredients such as salads, pasta dishes, sandwiches pastries and snack (Pham and Wang, 2017). In the same way, equine's milk allergic patients should be aware of cosmetic products which can contain mare's or donkey's milk proteins such as caseins, α-lactalbumin and β-lactoglobulin mentioned as « Equae lac ». Finally, as with other food allergies, there is always a risk of accidental exposures of allergens and allergic reactions. Consequently, preparedness is a critical aspect of management and Epinephrine auto-injectors and written emergency actions plans should be provided because severe reactions may cause death after fatal or near fatal anaphylaxis.

According to the reported cases, epinephrine was widely available for anaphylactic reactions caused by these severe allergies. For instance, one case report described a 5-year-old boy in who had a sample of Pecorino Romano cheese and developed anaphylaxis, requiring treatment with a total of 3 epinephrine doses (Pham and Wang, 2017). Furthermore, Al-Hammadi et al. (2010) reported an allergic 6-year-old boy who immediatly received epinephrine hydrocortisone, salbutamol, aminophylline and magnesium-sulfate once he had anaphylaxis caused by a selective allergy to camel's milk.

Finally, it can be confirmed that the burden of selective food allergies should be on de doctors, the consumers and patents (in case of allergic children). First, to confirm a food allergy and avoid unnecessary dietary restrictions, a diagnosis should be made by a doctor. Indeed, doctor diagnosed food allergies requires avoidance diets in order to avoid hypersensitivity symptoms. On the other hand, living with this disease leads to obstacles that are often significant. The daily burden and challenges of living with selective food allergies for the children and for their family, are overlooked and minimized. Food allergies cause significant financial strain and time burden for patiens and parents. For instance, for some families, daily realities and needs for caring for children with food allergy present a major financial burden of hypoallergenic formulas and frequent visits to doctors (Asthma and Allergy Foundation of America, 2019).

5. Conclusion

Milk from other mammalian species including goat's, sheep's, donkey's, mare's and camel's milk has been usually suggested as potential alternatives to cow's milk especially for patients with CMA. However, significant amino-acid sequence homology resulted high level of clinical cross-reactivity between milk from different mammalian species such as buffalo's, sheep's or goat's milk which are considered as an inappropriate feeding alternative for patients with CMA. Meanwhile, camelid's and equine's milk might be better tolerated, although further studies are needed on the allergenicity of alternative milk protein sources. Unlike CMA, selective mammalian milk allergies are unusual and rare food allergies of which only few allergic cases have been detected in the world. However, these rare allergies are characterized by severe symptoms which can be elicited even after the ingestion of small quantities mammalian milk and products. Furthermore, The number of cases are expected to increase in the future as the production and the consumption of different mammalian milk will continue to raise worldwide. According to the studied allergic cases, caseins are reported as the major allergens in goat's, sheep's and buffalo's milk and not whey proteins because the high caseins contents in caprine and ovine milk. Cheese products including Ricotta, Romano, Pecorino and Mozzarella, are considered as the most common source of allergens to mammalian allergic patiens, especially goat's, sheep's and buffalo's cheeses. On the other hand, whey proteins including lysozyme, α-lactalbumin and β-lactogloblin are reported to be the major allergens in donkey's and mare's milk despite their thermal sensitivity due to the low casein/whey proteins ratio in equine's milk.

Allergen avoidance and accessible emergency medications are the mainstay of management in food allergies. However, eliminating milk products from the diet can be difficult especially in case of cross-contamination and hidden milk ingredients. There is a strong need to promote awareness of various food ingredients and food products that are associated with adverse allergic reactions in order to protect sensitive consumers from unwanted exposure to offending food allergens.

CRediT authorship contribution statement

Roua Lajnaf: Conceptualization, Methodology, Software, Visualization, Investigation, Writing-Original draft preparation, Writing – review & editing. **Sawsan Feki:** Conceptualization, Visualization, Investigation, Software. **Salma Ben Ameur:** Conceptualization, Visualization, Investigation. **Hamadi Attia:** Supervision. **Thouraya Kammoun:** Supervision. **Mohamed Ali Ayadi:** Conceptualization, Supervision, Writing – review & editing. **Hatem Masmoudi:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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