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Review

Cow's milk alternatives for children with cow's milk protein allergy - Review of health benefits and risks of allergic reaction

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ABSTRACT

Cow's milk protein allergy (CMPA) is considered as the most common food allergy in early life and may cause anaphylaxis reactions in severe cases. This review summarises recent findings in CMPA studies, especially regarding the main relevant cow's milk substitutes such as hydrolysed and plant-based (soy and rice) formulas in addition to other mammalian milk types (goat, sheep, donkey, mare and camel) to reduce allergy risks for children. Extensively hydrolysed cow's milk formulas are mainly used as an alternative for children with CMPA, despite their poor palatability. Goat's and sheep's milk and soy-based formulas are not recommended because of their high cross-reactivity with cow's milk proteins. On the contrary, equine's and camel's milk proteins are suggested as suitable alternative solutions due to their low sequence identity levels with cow's milk proteins. Nonetheless, further research needs to confirm the usefulness of these milk types as a solution in paediatric CMPA.

Contents

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1. Introduction

Cow's milk is commonly an omnipresent and a basic food in human diet. It is the most complete food on the planet and the first ingested at an early age especially when breastfeeding is either not possible or insufficient to cover the nutritional needs of infants (Mukhopadhy & Sweeney, 2016; Solomon & Bondar, 2021). Nutritional richness of bovine milk and its dairy products (as yoghurt, cheese and fermented milk products) has been widely validated (Mozaffarian, 2019; Plessas, Bosnea, Alexopoulos, & Bezirtzoglou, 2012; Savaiano & Hutkins, 2021). They represent exceptional sources of nutrients as essential minerals and important vitamins (Khurana & Kanawjia, 2007; Kok & Hutkins, 2018). Cow's milk is also a good source of proteins characterised by a high biological value, polyvalent roles in immune-function as well as in the transport and the adsorption of nutrients (Fiat et al., 1993; Pereira, 2014; Qin, He, & Xu, 2009; Verduci et al., 2019; Zimecki & Kruzel, 2007).

Cow's milk and dairy products are the most widespread among all mammalian milk, representing approximately 81.26% of global world milk production according to the statistics of Food and Agriculture Organisation (FAO) (FAOSTAT, 2021). Cow's milk contains more than 200 different proteins, but they are not all antigenic (D'Auria et al., 2018). Cow's milk proteins are commonly classified according to their solubility, functionality and rheological properties in two main groups: caseins and whey proteins (Jost, 1993; Kinsella & Morr, 1984; Marinova et al., 2009).

Caseins are the main protein fraction accounting for ~80% of total milk proteins and can be obtained through acidification at pH 4.6, rennet coagulation or ultracentrifugation (Jensen, Poulsen, Møller, Stensballe & Larsen, 2012; Lajnaf, Picart-Palmade, Attia, Marchesseau & Ayadi, 2022c; Liang & Luo, 2020). They are mainly located in the micellar complexes consisting of four different caseins: α_{S1}-, α_{S2}-, β- and κ-casein representing 38%, 13%, 36% and 13%, respectively (Bramanti, Sortino, & Raspi, 2002; Davies & Law, 1980). Caseins are unstructured proteins, making them sensitive to proteolytic digestion and resistant to heat treatments (Kim, Wang, & Selomulya, 2020; Madadlou & Azarikia, 2013; Sadeghian et al., 2018).

On the other hand, whey proteins represent the soluble fraction of milk in which casein micelles are suspended. They are the second main component of cow's milk proteins constituting ~20% of the total proteins (Fox, 2008; Madureira, Tavares, Gomes, Pintado, & Malcata, 2010). Whey contains highly structured globular proteins. The β-lactoglobulin is the most abundant with a proportion of 50% of total whey proteins and has no homologue in human's milk (Brignon, Chtourou, & Ribadeau-Dumas, 1985; Marshall, 2004; Tai, Chen, & Chen, 2016). The β-lactoglobulin exists in milk as a dimer of 36 kDa held together by non-covalent interactions that makes it relatively resistant to enzymatic hydrolysis through digestive enzymes (Cases, Rampini, & Cayot, 2005; Guo, Fox, Flynn, & Kindstedt, 1995; Ma, Wang, & Guo, 2018). In contrast, this protein is sensitive to heat denaturation due to the presence of two intra-molecular disulfide bridges and a free sulphydryl (−SH) group in each monomer (Cases et al., 2005; Krishna et al., 2021; Sava, Van der Plancken, Claeys, & Hendrickx, 2005). α-Lactalbumin is the second major protein of cow's milk whey representing 25% of total soluble proteins in bovine milk. It is a small monomer of 14 kDa with a high sequence homology compared with its human counterpart (Lajnaf, Attia & Ayadi, 2022a; Lisak, Toro-Sierra, Kulozik, Božanić, & Cheison, 2013; O'Mahony & Fox, 2013). Whey contains also other minor proteins as immunoglobulins, bovine serum albumin (BSA) and lactoferrin. These proteins come from blood stream, whereas the β-lactoglobulin and the α-lactalbumin are directly synthesised in the mammary glands (Reynolds & Folley, 2016; Séverin & Wenshui, 2005).

Hence, cow milk is most universal in human nutrition, whereas milk composition differs considerably due to genetic factors, physiological factors, nutritional factors, frequency of milking, and environmental conditions. Cow's milk is largely consumed in practice due to required nutritional composition present in it and has good yield with huge population. However, the other milk sources are limited more in their usage due to less awareness and availability (Nayak, Ramachandra, & Kumar, 2020). Nutritionally, human milk is different from bovine milk in terms of both of protein content and composition. First, bovine milk contains a higher concentration of proteins than those of human milk with values of 3.2 g L^{-1} and 0.9−1.9 g L^{-1} for bovine and human milk, respectively (Claeys et al., 2014; Sabahelkhier, Faten, & Omer, 2012). Furthermore, human milk is deficient in β-lactoglobulin and lacks α_{S1}-casein that are the major milk proteins in soluble and micellar fractions of cow's milk, respectively (Wal, 1998) (Table 3). On the other hand, human's milk is comparable with horse's and donkey's milk, as it contains similar basic chemical compositions compared with other animal milk composition. Human's milk and donkey's milk are characterised by lower protein content when compared with sheep's, cow's, goat's, mare's and camel's milk that avoid an excessive renal load of solute (Nayak et al., 2020).

On average, human's milk contains a lower level of total protein and a lower casein/whey protein ratio (average of 26.06% for caseins and 53.52% for whey proteins) when compared with cow's milk. The high casein/whey ratio in cow's milk makes it an excellent matrix for cheese production, whereas it is believed to play a crucial role in the sensitisation to its protein fraction (Barłowska, Szwajkowska, Litwińczuk, & Król, 2011; Nayak et al., 2020).

In recent years, there has been a significant rise in the number of adults and children of all ages suffering cow's milk protein allergy (CMPA). Consequently, parents are influenced towards frequently choosing cow's milk alternatives for children, including other mammalian specie's and plant-based drinks. Up to now, there is no review available for cow's milk substitutes comprising the different nutritional and immunological aspects. Thus, in the present review, we sought to summarise the different investigations of cow's milk alternatives for patients with CMPA including hydrolysed cow's milk formulas, plant-based formulas and other milk from different mammalian species. This study covers the nutritional composition as well as the allergenicity seen by various authors.

2. Cow's milk allergy: state of the art

Despite its consumption all over the world, cow's milk can be responsible for allergic reactions caused by its protein components. Cow milk protein allergy (known as CMA or CMPA) is one of the most common food allergies, especially during childhood, affecting approximately 3−8% of the total paediatric population in different countries (Lajnaf et al., 2022a; Moen, Opheim, & Trollvik, 2019). It is the most common food responsible for anaphylaxis in young children (Cianferoni & Muraro, 2012). CMPA is ranked third among all food allergies responsible for serious anaphylactic reactions (8−15% cases) (Cianferoni & Muraro, 2012; Lajnaf et al., 2022a). Furthermore, CMPA caused the greatest number of fatal reactions to children according to the results of previous studies (Abrams & Sicherer, 2021; Fiocchi et al., 2010; Flom & Sicherer, 2019; Macdougall et al., 2002). For instance, eight children died of food-induced anaphylaxis in the UK over 10 years, four of them died from CMPA after eating milk and ice cream (Macdougal, Cant, & Colver, 2002).

The hypersensitivity reaction to bovine milk may involve both immunoglobulin E (IgE) or non-IgE mediated reactions (Pereira, 2014). IgE-mediated food allergy reaction is the best known and characterised type of food allergy (Yu, Freeland, & Nadeau, 2016).

Table 1
Enzymatic hydrolysis in infant formulas and reduction in antigenicity and allergenicity of milk proteins.

Substrate	Enzyme	Immunogenicity reduction	Reference
β-Lactoglobulin (Bos d5)	Trypsin alone or in combination with both of chymotrypsin and pepsin	50% decrease in the absorbance in ELISA tests without eliminating it.	Bonomi et al. (2003)
Milk proteins	Trypsin	Reduction of allergenicity of all milk proteins: patients with CMPA (n = 10), only 4/10 patients had IgE antibodies to undigested β-Lg	Haddad et al. (1979)
α-Lactalbumin (Bos d4) and β-lactoglobulin (Bos d5)	Chymotrypsin and pepsin	A 50% decrease in the absorbance in ELISA tests without eliminating it	Monaci et al. (2006)
Milk proteins	Alcalase; Protamex and Flavourzyme	The reduction of the allergenicity of caseins, β-lactoglobulin and α-lactalbumin.	Liang et al. (2021a)
		The reduction of allergenicity of caseins and β-lactoglobulin (IgE binding and IgG-binding ability) from 44.24% to 50.07% and 57.89% −92.51%, respectively	Liang et al. (2021b).
		The reduced the IgE binding capacity of milk proteins of more than 50%	Liang et al. (2022)
Caseins	Latex peptidases from three different species (*Calotropis procera*, *Cryptostegia grandiflora* and *Carica papaya*)	The reduction of allergenicity of caseins: no immune reactions in mice allergic to cow's milk, similar to a commercial milk hydrolysed formula.	Oliveira et al. (2019)
Whey protein isolate and milk protein concentrate	Actinidin protease from kiwi fruit	The reduction of allergenicity of β-lactoglobulin 43% in milk protein concentrate and 54% in whey protein isolate as shown by ELISA analysis	Kaur et al. (2022)
Whey protein concentrate	Papain and neutrase	The reduction of allergenicity of whey proteins	Nakamura et al. (1993) Nakamura et al. (1992)

Table 2
Cross reaction risks of plant-based drink alternatives and their health benefits.

Plant-based formula	Health benefits	Health issues	Cross reaction risks	References
Soy-based formulas	Tolerance in infants with CMPA. Normal growth, adequate protein nutritional status, and normal bone mineralisation in full-term infants.	Contains isoflavones characterised by an estrogenic action in the body of the infants leading to serious subsequent health problems such as reduction of fertility in males and earlier puberty in females.	Cross-reactivity between soy and cow's milk proteins: 25−60% of children with non IgE-mediated CMPA and 15% of children with IgE-mediated CMPA show cross reactivity with soy proteins. 14% of children with IgE-mediated CMPA below the age of 3.5 years (n = 93) show cross reactivity with soy proteins.	Muraro et al. (2002) Addou et al. (2016) Dhesi et al. (2020) Zeiger et al. (1999) Souroullas et al. (2018)
Rice-based formulas	Tolerance by allergic children with CMPA. Provide all essential nutrients already provided by hydrolysed milk formulas without any phytoestrogens or lactose. Suitable nutritional quality for infant's growth if it is supplemented by essential amino acids.	High concentrations of arsenic and lack of three essential amino-acids already found in human milk (tryptophan, threonine and lysine).	The least allergenic foods causing allergic reactions in less than 1% of children with CMPA.	Verduci et al. (2019) Alessandro Fiocchi et al. (2016) Hernández-Martínez and Navarro-Blasco (2013) Jackson et al. (2012) Souroullas et al. (2018) Verduci et al. (2019)
Almond formulas	Better than the other known alternatives like cow's milk hydrolysate and soy-based formulas in terms of nutritional quality. A source of monounsaturated fatty acids such as oleic acid and polyunsaturated fatty acids. High levels of vitamin E and other nutrients such as manganese, calcium, magnesium, potassium, iron, selenium, zinc and copper.	Unsuitable as the only food in infant diet. Should be fortified by adding calcium and Vitamin B12 that are essential for the growing need.	Almond proteins can also cause allergic reactions especially to allergic patients Efficient alternative of cow's milk in infants with CMPA and cow's milk intolerance: tolerance by children with CMPA (n = 26) at the age from 5 to 9 months.	Giovannini et al. (2014) Salpietro et al. (2005) Iacono et al. (2008) Vanga and Raghavan (2017)

IgE-mediated reactions occur immediately after milk ingestion due to an interaction between milk proteins and immune mechanisms and can be divided into two phases: a first sensitisation phase followed by an allergic reaction phase (Fig. 1).

The first exposure of milk allergens (Bos d 4 – Bos d 12) to allergic patient leads to thesensitisation phase. Antigen presenting cells (APC) take up the proteins and process them into smaller peptides, which they present on their surface MHC II molecules to

Table 3
Average concentration (g L^{-1}) of proteins in different mammalian milk types.[a]

Protein	Cow	Goat	Sheep	Donkey	Mare	Camel	Human
Caseins							
α_{S1}-CN	10.0–15.0	0–7.0	3.0–6.0	0.2–2.0	2.5	5.0	0.3–0.8
α_{S2}-CN	3.0–4.0	4.2	9.0–12.0	0.2	0.2	2.2	n.d
β-CN	9.0–11.0	11.0–18.0	19.0–28.0	3.9	11.0	15.0	1.8–4.0
κ-CN	3.0–4.0	4.0–4.6	4.0–5.0	n.d	4.6	0.8	0.6–1.0
Whey proteins							
β-Lg	3.0–4.0	2.1	5.6–7.2	3.2–3.7	3.0	n.d	n.d
α-La	1.0–1.5	1.2	1.7	1.8–3.0	3.3	3.5	1.6

[a] Abbreviations are: α_{S1}-CN, α_{S1}-casein; α_{S2}-CN, α_{S2}-casein; β-CN, β-casein; κ-CN, κ-casein; β-Lg, β-lactoglobulin; α-La, α-lactalbumin; n.d, not detected. Data are from: Hinz et al. (2012); Kappeler et al. (2003); Lajnaf et al. (2020); Malacarne et al. (2002); Miranda et al. (2004); Wal (1998).

T-cell receptors (TCR) on naïve T cells specific for the particular peptide (Broekman, Eiwegger, Upton, & Bøgh, 2015). A naïve T cell is the appelation of a T cell that has matured and been released by the thymus, but has not yet encountered its corresponding antigen. In other words, naïve T cells are in the stage between maturity and activation. Indeed, each naïve T cell has a unique TCR that recognises a specific antigen (Mak, Saunders, & Jett, 2013; Zhan, Carrington, Zhang, Heinzel, & Lew, 2017).

T cells are activated upon further signalling events that cause the naïve T cells to differentiate into Th2 cells that produce cytokines like IL-4 and IL-13. This in turn leads to promotion of B cell differentiation into IgE-producing plasma cells as well as intestinal mast cell proliferation and accumulation known as mastocytosis (Divekar & Kita, 2015; Stark, Tibbitt, & Coquet, 2019). Secreted food allergen-specific IgE binds to the high-affinity FcεRI receptors that are located on the surface of tissue mast cells (Broekman et al., 2015).

The second allergic reaction phase takes place upon subsequent exposures to the same allergens, where allergens interact with IgE that are previously located at the surface of mast cells and linked through FcεRI receptors resulting in their degranulation and release of inflammatory mediators, such as histamine prostaglandin E2 (PGE2) and 5-hydroxytryptamine (5HT) inducing the resulting symptoms such as hives, vomiting, swelling and breathing difficulty (Fig. 1).

Unlike the immediate IgE mediatted reactions, the non-IgE mediated reactions are delayed taking up between 1 h and several days after ingestion of cow's milk to develop, but they still involve the immune system (Ekezie, Cheng, & Sun, 2018; El-Agamy, 2007; Izadi, Khedmat, & Mojtahedi, 2019; Mansouri, 2015; Vandenplas et al., 2007; Walsh, Meyer, Shah, Quekett, & Fox, 2016).

Overall, children with food allergy in early life show an altered faecal microbiota as well as lower microbiota diversity when compared with healthy controls (Fig. 1). For instance, children with food allergy showed significantly decreased numbers of bacteroidetes and a significantly increased number of firmicutes compared with healthy children. Meanwhile, the most differentially abundant faecal taxa in children with food allergy were characterised by increased abundances of *Clostridium* IV and *Subdoligranulum* (Clostridia class and decreased abundances of *Bacteroides* and *Veillonella* (Clostridia class) (Chen, Chen, Kong, Chang, & Huang, 2016). However, CMPA for children is characterised by in an enriched taxa from the *Clostridia* class and *Firmicutes phylum* (Bunyavanich et al., 2016).

Cow's milk contains numerous different proteins that can trigger allergic reactions, and includes caseins (also called Bos d8) and whey proteins (Bu, Luo, Chen, Liu, & Zhu, 2013). Casein (Bos d8) consists of α_{S1}-casein (Bos d9), α_{S2}-casein (Bos d10), β-casein (Bos d11) and κ-casein (Bos d12), while whey proteins include not only major allergens such as α-lactalbumin (Bos d4) and β-lactoglobulin (Bos d5) but also minor allergens such as BSA (Bos d6), immunoglobulins (Bos d7) and lactoferrin (Bos d lactoferrin) (D'Auria et al., 2018; Hochwallner, Schulmeister, Swoboda, Spitzauer, & Valenta, 2014; Lajnaf, Feki, Attia, Ayadi, & Masmoudi, 2022b). Previous work confirmed that the most common allergens that are detected in patients with CMPA are caseins (especially α_{S1}-casein), β-lactoglobulin and α-lactalbumin (D'Auria et al., 2018). Patients with CMPA are commonly sensitised to one or more allergens. Indeed, only 27% of patients with CMPA present sensitisation to only one allergen, while 15% are allergic to two cow's milk allergens, 20% are allergic to three allergens, 22% are allergic to four allergens and finally 16% are sensitised to five allergens. Since birth, IgE response against β-lactoglobulin precedes those against caseins and α-lactalbumin. However, IgE response against caseins becomes predominant before the age of one year, while the IgE response to α-lactalbumin appears only after the age of one year (Boutin, Liabeuf, Agabriel, Cleach, & Vitte, 2015).

Overall, caseins are usually considered as the main allergen among all milk proteins (especially α_{S1}-casein) which is associated to its high content (80% of total proteins, about 30 g L^{-1} bovine milk) (D'Auria et al., 2018). Due to its strong heat stable property, casein has become the most prevalent allergen in bovine milk (Cheng, Yang, Ni, Peng, & Lai, 2017; Jiang et al., 2019); in contrast to whey proteins, caseins are thermostable and thus retain allergenicity after extensive heat treatment (Xu, Shi, Yao, Jiang, & Luo, 2016). They do not degrade with heating at high temperature probably due to their lack of secondary structure or their micelle composition, which could explain their high allergenicity (Maryniak, Sancho, Hansen, & Bøgh, 2022).

Other works reported that the β-lactoglobulin is considered as the most potent cow's milk allergen for children sensitive to milk protein, being responsible for allergic reactions in 60–80% of CMPA patients, as this protein does not have a counterpart in human milk (Stöger & Wüthrich, 1993). Several researches confirmed the β-lactoglobulin as the main allergen representing 66% of milk allergy cases, followed by caseins (57%), α-lactalbumin and BSA (representing together 18% of total cases) (Miciński et al., 2013; Peñas, Snel, Floris, Préstamo, & Gomez, 2006).

Children are more affected by CMPA than adults due to the induction of oral tolerance that occurs during the development of the individual. Oral tolerance is defined as the process in which the immune system promotes systemic non-responsiveness to antigens that are administered orally (Vickery, Scurlock, Jones, & Burks, 2011). Researchers report that children (80–90%) possessing allergenicity to cow's milk proteins are found to be tolerant after the age of 5 years due to the maturation of immune and digestive systems at this age (Crittenden & Bennett, 2005; Fiocchi et al., 2008; Sjögren, Jenmalm, Böttcher, Björkstén, & Sverremark-Ekström, 2009). Gut colonisation and the diversity and intensity of microbial exposure can play an important role in inducing cow's milk tolerance. Maternal microbiota forms the first microbial inoculum, and from birth, but the microbial diversity increases and converges toward an adult-like microbiota by the end of the first 3–5 years of life. The gut microbiota changes greatly during the first

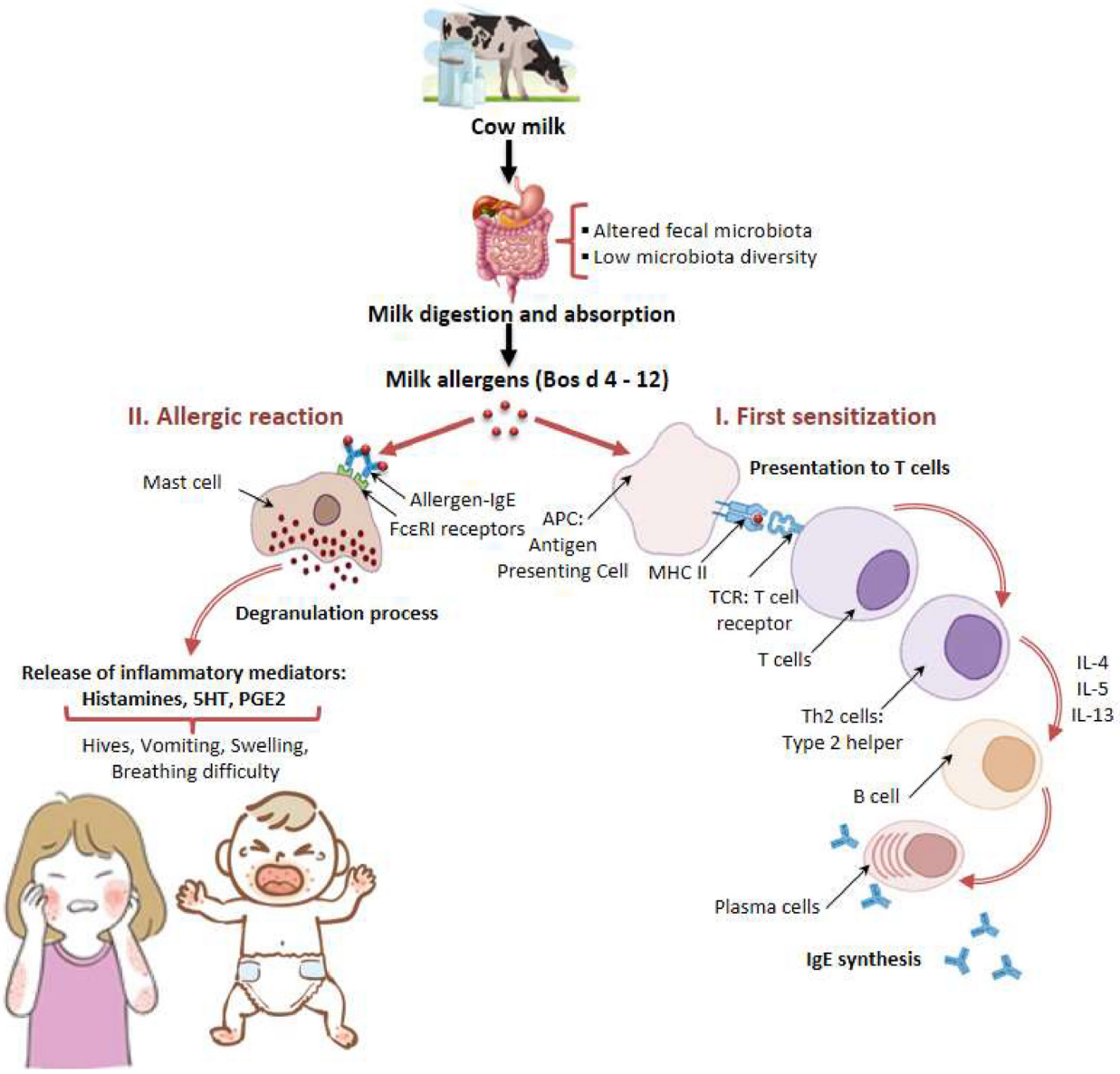

Fig. 1. Classical immune mechanism of IgE-mediated cow milk allergy (CMPA). Naïve CD4 T cells differentiate into Th2 cells by milk proteins (Bos d4- Bos d12) and produce type-2 cytokines like IL-4, IL-5 and IL-13. These cytokines promote B cells differentiation into IgE-producing plasma cells. Milk allergen-specific IgE is distributed systemically and binds to the high-affinity IgE receptor (FcεRI) on mast cells. After sensitisation, cross-linking of re-exposed milk allergens to allergen-specific IgE that binds to FcεRI on mast cells induces degranulation of mast cells and the release of various inflammatory mediators such as histamines, 5-hydroxytryptamine (5HT) and prostaglandin E2 (PGE2).

years of life and is relatively stable and mature after 5 years of age (Rodríguez et al., 2015; Roswall et al., 2021). A more diverse gut microbiota early in life might prevent allergy development and lead to tolerance. Indeed, intestinal bacterial flora play a crucial role in generating a Th2 cell population whose size and response are adequately regulated and hence, fully susceptible to oral tolerance induction for children with CMPA at the age of 5 years (Crittenden & Bennett, 2005; Rodríguez et al., 2015; Sjögren et al., 2009; Sudo et al., 1997; Yang et al., 2021).

3. Cow's milk alternatives in CMPA

The basic treatment of CMPA consists of strict elimination of milk and dairy products from the diet. In case of accidental exposure, different possible of medical treatments could be used depending on the severity of the clinical features. However, this deprivation of bovine milk and dairy products from the paediatric diet increases nutritional risk in children, because of their importance as the most complete food and the main source of proteins, fats, minerals and vitamins (Comberiati et al., 2015; Groetch & Nowak-Wegrzyn, 2013; Verduci et al., 2019).

During last decades, several studies have been interested and this problem has been widely discussed in this issue leading to many possible alternatives to cow's milk that are validated and currently used or still under evaluation (Dupont et al., 2020; El-Agamy, 2007; Isolauri et al., 1995; Kipfer & Goldman, 2021; Muraro, Giampietro, & Galli, 2002). These valuable alternatives could be classified into three major classes: hydrolysed cow's milk formulas, plant-based and mammalian milk alternatives (Maryniak et al., 2022) (See Fig. 2).

3.1. Hydrolysed cow's milk formulas

Two main groups of hydrolysed cow's milk formulas could be consumed. The first group is the extensively hydrolysed cow's milk

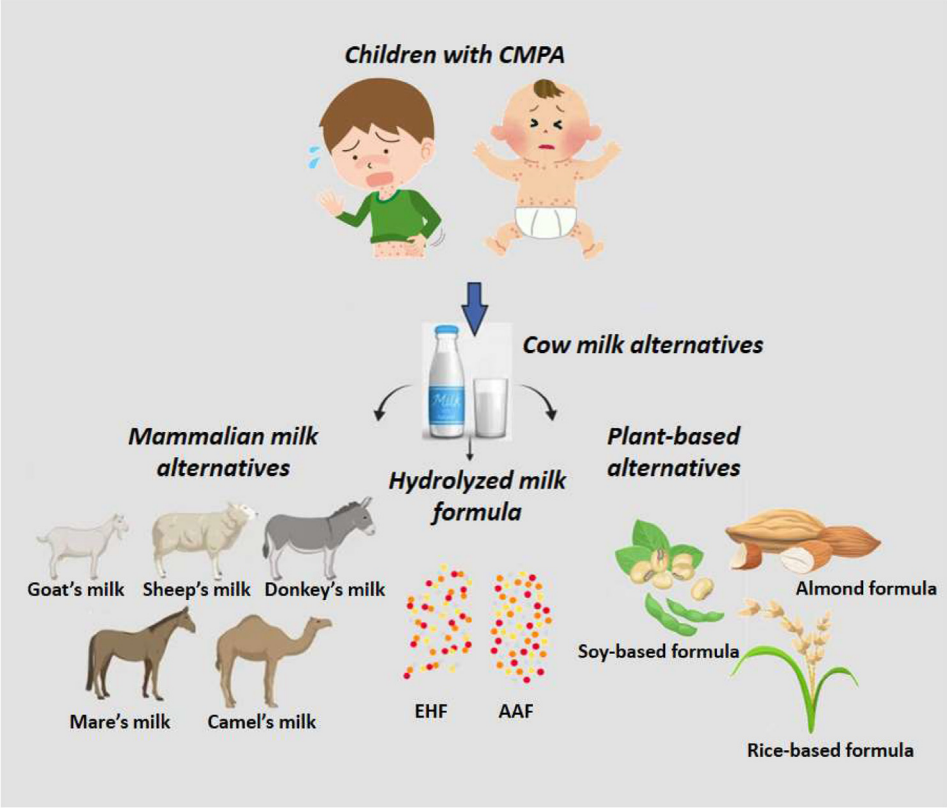

Fig. 2. Different sources of cow's milk alternatives for infant formula manufacture for infants with cow's milk protein allergy (CMPA). Abbreviations: EHF, enzymatic cow's milk hydrolysates; AAF, amino acid-based formulas.

protein-based formulas (EHF) that are derived from bovine caseins or whey proteins and tolerated by approximately 95% of cow's milk allergic patients. The second group consists of amino acid-based formula (AAF) and is composed of synthesised free amino-acids that are tolerated by the majority of allergic patients (Bahna, 2008).

3.1.1. Extensively hydrolysed cow's milk protein-based formulas

EHF were primarily prepared via proteinases from different sources that are used singly or in combination including digestive enzymes (pepsin, trypsin, and chymotrypsin), plant-based enzymes (papain and bromelain), and microbial sources (alcalase and substilisin) (Table 1) (Abd El-Salam & El-Shibiny, 2021).

The use of these enzymes was carried out to cow's milk proteins to imitate the digestion process leading to the reduction of the intestinal and enzymatic activities in newborns (Miciński et al., 2013; Monaci, Tregoat, van Hengel, & Anklam, 2006). Currently, EHF are recommended as formulas of choice for the nutrition of infants with CMPA as they are not only well tolerated but also nutritionally adequate (Isolauri et al., 1995; Klemola et al., 2002; Stróżyk, Horvath, Meyer, & Szajewska, 2020). However, the major disadvantages of EHF are their bitter taste and their high financial cost (Høst, 1994; Maehashi, Matsuzaki, Yamamoto, & Udaka, 1999; Maslin, Fox, Chambault, & Meyer, 2018; Miraglia Del Giudice et al., 2015). Bitterness of EHF is caused by the presence of peptides lower than 1000 Da, containing hydrophobic amino acids, especially when their amino and carboxyl groups are involved in peptide bonds, which makes these hypoallergenic formulas unpalatable for children with CMPA (Cheison, Wang, & Xu, 2007; de Carvalho et al., 2019; Leksrisompong, Miracle, E., & Drake, 2010).

EHF can potentially cause allergic reactions to 5–10% of cases because of the presence of short peptides sequences with potential immunogenic capacities. Hence, EHF are not recommended for children with either severe allergic reactions to cow's milk proteins or a history of anaphylaxis (Fiocchi et al., 2016; Koletzko et al., 2012; Verduci et al., 2019).

It was reported that hydrolysis of β-lactoglobulin only by trypsin or by the combination of this enzyme with pepsin and chymotrypsin reduces partially its allergenicity. The allergenicity of β-lactoglobulin is significantly reduced when the combined methods (enzymatic hydrolysis and heat treatment) were applied on the protein (Bonomi et al., 2003; Monaci et al., 2006). Pepsin and α-chymotrypsin are considered the most efficient enzymes used in combination for the reduction of allergenicity of both α-lactalbumin and β-lactoglobulin. Overall, the degree of hydrolysis of these hydrolysates ranged between 1% and 20% depending on the enzyme combination and the hydrolysis time (Miciński et al., 2013; Monaci et al., 2006). EHF production should be performed in appropriate hydrolysis conditions. Indeed, the degradation of proteins should not be extensive to avoid taste bitterness (Ziajka & Dzwolak, 1994). Caseins (α- and β-caseins) are reported to be sensitive to trypsin digestion, whereas whey proteins as α-lactalbumin, immunoglobulins and bovine serum albumin are not (Monaci et al., 2006; Nakamura, Sado, Syukunobe, & Hirota, 1993; Salami et al., 2008).

The rise in consumption and the commercialisation of cow's milk hydrolysates led manufacturers use new types of enzymes such as bacterial or fungal enzymes characterised by a higher specificity (Abd El-Salam & El-Shibiny, 2021; Miciński et al., 2013). Currently, the production of EHF involves the use of enzymatic preparations containing endo and exo-peptidases. These enzymes were found to improve the characteristics of EHF including both of organoleptic and antigenic characteristics (Abd El-Salam & El-Shibiny, 2021;

Raksakulthai & Haard, 2003). These preparations lead to the hydrolysis of hydrophobic peptides that are responsible for the allergenic potential of cow's milk proteins (Miciński et al., 2013).

Regarding the industrial process, the effectiveness of these enzymes was also increased when reactor systems were used instead of classical batch reactors. Indeed, hydrolysis of cow's milk proteins in these systems is continuous by the use of immobilised enzymes as endo and exo-peptidases (Miciński et al., 2013; Raksakulthai & Haard, 2003). Another innovative technique of preparing hypoallergenic EHF was reported involving hydrolysis with probiotics. Probiotics such as *Bifidobacterium lactis*, *Lactococcus lactis* and *Lactobacillus rhamnosus* were reported to reduce the allergenicity of cow's milk proteins. They can even reduce the severity of atopic dermatitis in breast-fed infants within two months of treatment (Adel-Patient et al., 2005; Isolauri, Arvola, Sütas, Moilanen, & Salminen, 2000; Miciński et al., 2013) as they participate in mucosal degradation of different macromolecules, leading to reduced allergenicity (Pessi, Sütas, Marttinen, & Isolauri, 1998). Furthermore, probiotics counteract inflammatory responses beyond the intestinal milieu. The combined effects of different probiotic strains such as *B. lactis* will guide infants when sensitisation to newly encountered antigens is initiated (Isolauri et al., 2000).

The effect of enzymatic hydrolysis on the allergenicity of milk proteins was thoroughly studied by various authors (Table 1). For instance, Bonomi et al. (2003) revealed that the allergenicity of the β-lactoglobulin (Bos d5) was reduced by hydrolysis using trypsin alone or in combination with both chymotrypsin and pepsin, resulting in a 50% decrease in the absorbance in ELISA tests without eliminating it. On the other hand, the combination of α-chymotrypsin and pepsin is considered as the most effective combination of enzymes in the reduction of allergenicity due to its selective proteolysis of both allergens α-lactalbumin (Bos d4) and β-lactoglobulin (Bos d5) with a degree of hydrolysis (DH) of 1−20% and depending and incubation time (Monaci et al., 2006). In the same way, the hydrolysis of milk proteins using trypsin led to the reduction of allergenicity of all milk proteins that were tested on 10 allergic patients. Among these patients, only 4/10 patients had IgE antibodies to undigested β-Lg (Haddad, Kalra, & Verma, 1979). Liang et al. (2021b) reported the allergenicity of caseins, β-lactoglobulin and α-lactalbumin was reduced after enzymatic hydrolysis using alcalase and Protamex. The hydrolysis process using these enzymes led to higher DH compared with those of neutrase, pepsin and papain inducing increasing levels of low molecular mass (<3 kDa). The use of alcalase, protamex and flavourzyme in the hydrolysis of cow's milk protein reduced the IgE binding capacity with a reduction rate of 56.31%, 50.62% and 56.45%, respectively (Liang et al., 2022). The enzymatic hydrolysis with alcalase, protamex and flavourzyme reduce the IgE binding and IgG-binding ability of caseins from 44.24% to 50.07% and 57.89%−92.51%, respectively (Liang et al., 2021a).

Some plant-based proteases are approved to be used in the production of food grade protein hydrolysates including most of the proteins in cow's milk that cause allergies. The latex peptidases from three different species (*Calotropis procera*, *Cryptostegia grandiflora* and *Carica papaya*) were reported to able to perform total hydrolysis of caseins after 30 min. These hydrolysates showed no immune reactions in mice allergic to cow's milk with a similar behaviour to a commercial partially hydrolysed formula. Furthermore, these plant based proteases showed a significant hydrolysis activity towards whey proteins, especially after heat treatment leading to an important reduction of allergenicity of these proteins (Oliveira et al., 2019). On the other hand, actinidin, which is a plant protease from kiwi fruit, was reported to significantly reduce the allergenicity of milk proteins including β-lactoglobulin in both of whey protein isolate and milk protein concentrate within the degree of hydrolysis from 9% to 16% at 60 °C and during 5 h (Kaur, Huppertz, & Vasiljevic, 2021). Both β-lactoglobulin and α_{S1}-casein undergo significant reduction in their allergenicity due to cleavage of conformational epitopes with higher degrees of hydrolysis using actinidin. For instance, an hydrolysis at 60 °C during 5 h led to an antigenicity reduction of β-lactoglobulin of ~43% in milk protein concentrate and ~54% in whey protein isolate as shown by enzyme-linked immunosorbent assay (ELISA) analysis (Kaur, Huppertz, & Vasiljevic, 2022). Some plant proteases, including papain, were recently assessed for reduction of milk's antigenicity with a hydrolysis degree ranging from 0.16% to 27.80%. Nakamura et al. (1993) showed that combination of papain and neutrase in hydrolysis was more effective in reducing the allergenicity of whey protein when compared with the use of a single enzyme. In another study, the addition of papain to whey protein concentrate hydrolysates already prepared with alcalase was reported to improve the sensory properties of the obtained hypoallergenic formulas by reducing bitterness (Wróblewska et al., 2004).

3.1.2. Amino acid-based formulas

Considering the AAF, these interesting alternatives provide protein in free amino-acid form to allergic patients: they are considered as the only non-allergenic milk formulas. AAF are distinguished by extreme allergenic safety especially when the other formulas are not tolerated (Verduci et al., 2019).

Unlike EHF, AAF are based on free amino acids and are totally free from peptides derived from cow's milk proteins. Overall, AAF are used as the second choice for children with severe CMPA if clinical symptoms occur with the use of EHF (Meyer, Groetch, & Venter, 2018). AAF formulas are also used for the nutrition of infants with multiple food allergies, allergic symptoms, or severe atopic eczema when exclusively breastfed, severe forms of non-IgE mediated cow's milk allergy such as eosinophilic esophagitis, enteropathies, and food protein-induced enterocolitis syndrome (Isolauri et al., 1995; Miraglia Del Giudice et al., 2015).

Hypoallergenicity of AAF has been previously confirmed by several in vivo analysis showing that these formulas are well tolerated by children suffering from severe CMPA (Nowak-Węgrzyn, Czerkies, Collins, & Saavedra, 2015; Sicherer et al., 2001). Nutritionally, previous works reported that the infants fed with AAF showed a normal growth rate when comparing with those fed with other types of infant formulas, which concluded that AAF formulas support a normal growth of children (Canani et al., 2017).

Unfortunately, the drawbacks of these formulas are their low palatability and high cost (Bahna, 2008; Miraglia Del Giudice et al., 2015; Verduci et al., 2019). Miraglia Del Giudice et al. (2015) reported through sensory evaluation of hydrolysed cow's milk formulas including EHF of whey and caseins as well as AAF. These authors noted that EHF of whey proteins were judged of better palatability than AAF and casein EHF. Bitterness in proteins is rare, but some amino acids can have bitter properties including isoleucine, valine and L-enantiomer of proline. Amino acid bitterness is attributed to the size, shape, and hydrophobic character of the R group (Zeece, 2020).

3.2. Plant-based alternatives

Non-dairy products are currently very promising and useful widely. They are considered as the best nutritional choice due to their natural and healthy aspects. Medical (lactose intolerance, CMPA, hypercholesterolaemia and coronary heart diseases) and nutritional factors (bioavailability of more amounts of vitamins, minerals and dietary fibres) have led to the increase of

consumption of these products (Verduci et al., 2019). Most known and consumed plant-based drinks are manufactured from soy, almond, rice and coconut (Table 2) (Vanga & Raghavan, 2018).

3.2.1. Soy-based formula

Overall, soy-based formulas are well tolerated by children with CMPA (Muraro et al., 2002). However, many nutritional deficiencies with these formulas have been previously reported (Fiocchi et al., 2016). Actually, soy formulas are supplemented with appropriate quantities of nutrients including amino acids such as methionine, taurine, and carnitine. Soy based formulas are not deficient in minerals such as iron, calcium, zinc and phosphorus (Fiocchi et al., 2016; Verduci et al., 2019).

Despite these initiatives to improve the nutritional quality of soy-based formulas to meet the needs of children with CMPA, concerns have been raised regarding potential risks for the infant's health. Most of studies do not recommend the consumption of soy-based formulas for children with CMPA because of the recognition of soy proteins by IgE from CMPA patients. Indeed, approximately 25−60% of children with non IgE-mediated CMPA and 15% of children with IgE-mediated CMPA show cross reactivity with soy proteins (Addou et al., 2016; Dhesi, Ashton, Raptaki, & Makwana, 2020). Furthermore, soybean proteins P34 was mostly recognised by IgE antibodies from the sera of milk allergic patients (n = 10), with positive cutaneous test with P34 in the milk allergy mouse model. This soybean protein shares epitopes with bovine caseins, which is responsible for cross reaction between soybean and milk proteins (Candreva et al., 2015).

On the other hand, different studies have shown lower yet varying cross-reaction results, revealing clinically relevant reactions to soy or soy-based infant formulas (Table 2) (Maryniak et al., 2022). For instance, randomised controlled trial children with confirmed CMPA (n = 170) reported allergic responses in 10% of infants fed soy-based formula. Adverse reactions to soy were similar in both of IgE-mediated and non-IgE−mediated CMPA, and reactions were more common in infants below the age of 6 months (Klemola et al., 2002). In the same way, Zeiger et al. (1999) reported that 14% of children with IgE-mediated CMPA below the age of 3.5 years (n = 93) showed cross reactivity with soy proteins.

In addition to allergic reactions, soy-formulas contain isoflavones characterised by an estrogenic action in the body of the infants leading to serious subsequent health problems such as reduction of fertility in males and earlier puberty in females (Souroullas, Aspri, & Papademas, 2018; Strom et al., 2001). Consequently, soy-formulas were not recommended to infants during the first six months of their life either by European Academy of Allergy and Clinical Immunology (EAACI) or by European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) because of these different nutritional issues (Dhesi et al., 2020; Koletzko et al., 2012; Muraro et al., 2014). Researches revealed that EHF and AAF could be preferred over soy-formulas. Thus, infants with CMPA can be fed either EHF or AAF during the first year of life followed by the ingestion of soy-formulas after this period (Souroullas et al., 2018).

3.2.2. Rice-based formulas

Rice-formulas in their native and hydrolysed forms are also suggested as a potential plant-based alternative for children with CMPA as rice is one of the least allergenic foods (Bocquet et al., 2019; Verduci et al., 2019). For this reason, hypoallergenic formulas containing hydrolysed rice proteins have been developed and have now been in use for more than a decade in several countries (Maryniak et al., 2022).

Rice is reported to cause allergic reactions in less than 1% of children with CMPA; rice-formula is tolerated by allergic children (Bocquet et al., 2019; Helm & Burks, 1996; Verduci et al., 2019), providing all essential nutrients already provided by EHF without any phytoestrogens or lactose. Hence, hypoallergenic rice-based formula is being currently developed in various countries (D'Auria, Mandelli, Ballista, Di Dio, & Giovannini, 2011; Souroullas et al., 2018; Verduci et al., 2019). The nutritional quality of rice proteins is reported to be totally suitable to be used in infant formulas if it is supplemented by certain amino acids that can be lacking including lysine, threonine, tryptophan, carnitine and taurine (Fiocchi et al., 2016). Furthermore, hydrolysis is required to facilitate water solubility and digestibility of rice proteins (Bocquet et al., 2019). This hydrolysis leads to a low allergenicity of rice and to the absence of the cross-allergy between milk proteins and rice proteins. Hence, these formulas are adapted to the diet of children with CMPA, which explains their growing use in some countries (Maryniak et al., 2022).

Previous studies evidenced the absence of cross-reactivity between rice formulas and cow's milk proteins which makes these formulas well tolerated by children with CMPA (Table 2). However, only a limited number of cases of allergic responses toward hydrolysed rice-based formulas has been implied (Dupont et al., 2020). For instance, cow's milk allergic children showed reactivity to the hydrolysed rice-based formulas with specific IgE >0.35 kU L^{-1} or with positive in vivo studies through skin prick test. On the other hand, no reactivity was found with hydrolysed rice-based to children with CMPA (Fiocchi et al., 2003, 2006; Reche et al., 2010).

Although several studies have shown the rice-based formulas to be nutritional and allergy safe, they are still recommended as a second choice because of many patients who find these formulas unpleasant or not tolerated especially to children with severe forms of CMPA (Agostoni & Elvira, 2012).

Furthermore, these formulas contain high concentrations of arsenic (As) and lack three essential amino-acids already found in human milk. Consequently, rice drink is generally supplemented with tryptophan, threonine and lysine (Hernández-Martínez & Navarro-Blasco, 2013; Jackson, Taylor, Punshon, & Cottingham, 2012; Souroullas et al., 2018; Verduci et al., 2019).

3.2.3. Almond formulas

Almond drink was also suggested and introduced as suitable alternative milk to children suffering from CMPA and lactose intolerance. It is reported to be even better than the other known alternatives like cow's milk hydrolysate and soy-based formulas (Vanga & Raghavan, 2018).

Almond drink has less protein content than that of bovine milk, but similar amounts of carbohydrates and fats. It is a source of monounsaturated fatty acids such as oleic acid and polyunsaturated fatty acids. Almond drink presents a high nutritional quality as it has good levels of vitamin E and other nutrients such as manganese, calcium, magnesium, potassium, iron, selenium, zinc and copper, making it better than other plant-based beverages in terms of nutritional quality (Giovannini et al., 2014). This nutritional composition of almond drink makes it unsuitable to cover the growing needs of infants. Hence, it should be fortified by adding other micronutrients including calcium and vitamin B12 (Singhal, Baker, & Baker, 2017).

Therefore, almond drink has been shown that can provide adequate nutrients to the consumer, whereas almond proteins can also cause allergic reactions especially to allergic patients (Iacono, Lospalluti, Licastro, & Scalici, 2008; Vanga & Raghavan, 2017).

One randomised trial found that almond drink was well tolerated by children with CMPA (n = 26) at the age from 5 to 9 months, leading to suggest that this plant-based drink may an efficient alternative of cow milk in infants with CMPA and cow's milk intolerance (Salpietro et al., 2005). However, further in vitro and

in vivo studies are needed to confirm the suitability of almond drink for infants with severe CMPA.

Other vegetable protein sources are also available such as coconut, lupine, hemp and pea drinks, whereas theses preparations are not recommended for children under two years old (Souroullas et al., 2018).

3.3. Mammaliam milk alternatives

3.3.1. Goat's milk

According to the latest Food and Agriculture Organisation statistics, goat (*Capra hircus*) milk production in the world is reported to be about 20.6 million tons per year representing 2.26% of total milk production worldwide (FAOSTAT, 2021).

Goat's milk is characterised by a similar nutritional composition compared with that of bovine milk including proteins, fats, lactose and minerals. However, fat and proteins fractions of goat's milk are characterised by a higher digestibility when compared with that of cow's milk (Ceballos et al., 2009; Hinz, O'Connor, Huppertz, Ross, & Kelly, 2012; Verduci et al., 2019). Goat's milk contains similar amounts of trans fatty acids and saturated fats with cow's milk; it contains a higher amount of short-chain, and medium-chain fatty acids (C6–C10) than those of bovine milk.

Goat's milk and its products have long been a potential alternative (and still being considered in some countries) to patients with CMPA (Jandal, 1996; Maryniak et al., 2022; Park, 1994). Indeed, it lacks of α_{S1}-casein suggesting the possible use of this milk as an alternative to children with CMPA (Table 3). However, this substitution is not currently recommended because of the strong sequence homologies between bovine and caprine milk proteins varying between 82.4% (κ-casein, Bos d12) and 96.3% (β-lactoglobulin, Bos d5) (Table 4).

Several researchers have reported difficulty in tolerance of goat's milk proteins to children with CMPA because of cross-reactivity between caprine and bovine milk proteins through both of in vitro and in vivo assays (Table 5). For children at the age below 80 months (n = 21), in vitro immunoblotting assays showed that caseins in goat's milk are mainly identified by specific IgE binding among all goat's milk proteins (Gjesing, Østerballe, Schwartz, Wahn, & Lowenstein, 1986). In vivo studies showed that all children (n = 26) aged 5 months to 7 years with IgE-mediated CMPA had positive skin test responses to both bovine and caprine milk. In the same way, 92% of allergic children (n = 58) with a median age of 11 months had positive double-blind placebo test to fresh goat's milk (Bellioni-Businco et al., 1999; Bernard, Créminon, Yvon, & Wal, 1998). Bellioni-Businco et al. (1999) noted that the dose of goat's milk necessary to induce a reaction in patients with CMPA is significantly higher than that of cow's milk. Furthermore, in addition to allergic reaction risks, children with atopic dermatitis and CMPA who consumed goat's milk did not show any improvement in their clinical symptoms contrary to children who consumed donkey's milk (Vita et al., 2007).

These data indicate that goat's milk is not an appropriate cow's milk substitute for children with CMPA at the age ranging from one month to 7 years as reported by the previous works despite the low content of α_{S1}-casein in this milk (Table 5). For this reason, a warning on the lack of safety of goat's milk for children with CMPA should be on the label of goat's milk formulas to prevent severe allergic reactions in babies with CMPA.

Actually, goat's milk based formulas have received approval from EFSA for sale in European countries. These formulas seem to be a possible alternative for the nutrition of healthy children. However, EFSA's scientific opinion is not clear concerning the potential impact of the goat's milk-based formulas consumption on the subsequent development of a food allergy. Thus, further studies are required to make definitive conclusions, particularity the degree of severity of allergic reactions against goat's milk proteins for children who have received goat's milk-based formulas compared with those who have received cow's milk (EFSA, 2012).

Unlike CMPA, selective mammalian milk allergy to goat's milk is uncommon and has been reported only as case reports. Goat's milk allergy not associated with CMPA is reported as a rare disorder in which caseins are considered as the major allergen inducing symptoms especially α_{S1}-, α_{S2}- and β-caseins (Table 5) (Tavares, Pereira, Rodrigues, Loureiro, & Chieira, 2007).This particular allergy includes patients who are mostly older than those who are allergic to cow's milk and with a multiple allergy syndromes (to at least 3 foods). Clinical symptoms are often associated with more severe manifestations than those of other food allergies (Bidat, 2010). The low α_{S1}-casein content of goat's milk modifies the structure of caseins micelles and the ability of form a softer and more digestible coagulum in the stomach than that obtained with cow's milk. Indeed, the digestion of α_{S1}-casein begins with a partial degradation by human gastric juice, and then total hydrolysis with duodenal juice. This indicates that goat's milk with a low level of α_{S1}-casein takes a lower time to be degraded than milk with higher contents of this protein (Almaas et al., 2006). Hence, a better digestibility of goat's milk than that of cow's milk can then limit the amounts of allergens reaching the digestive mucosa of the host in intact form. Concerning whey proteins, caprine β-lactoglobulin, which is the major whey protein in both of caprine and bovine milk is reported to be hydrolysed more rapidly than its bovine counterpart (Almaas et al., 2006). Recently, Zhang et al. (2022) noted that structural differences between bovine and caprine α_{S1}-casein leads to higher allergenicity for cow's milk α_{S1}-casein compared with its caprine counterpart., as a significant increase of IgE and Th2 cell-related inflammatory factors, the proportion of Th2, and the expression of Th2 cell-related transcription factors was observed.

Table 4
Sequence identity (%) between cow's milk proteins and their counterparts in milk of different mammalian species.[a]

Protein	Cow	Goat	Sheep	Donkey	Mare	Camel	Human
Caseins							
α_{S1}-CN	100%	86.9%	87.4%	39.0%	38.2%	40.5%	26.6%
α_{S2}-CN	100%	87.5%	88.0%	56.1%	53.1%	50.0%	n.d
β-CN	100%	90.9%	91.4%	53.1%	53.1%	63.8%	49.3%
κ-CN	100%	82.4%	82.5%	51.8%	51.4%	53.5%	49.4%
Whey proteins							
β-Lg	100%	96.3%	95.7%	56.2%	57.4%	n.d	n.d
α-La	100%	94.3%	96.7%	71.5%	72.4%	69.1%	75.6%

[a] Abbreviations are: α_{S1}-CN, α_{S1}-casein; α_{S2}-CN, α_{S2}-casein; β-CN, β-casein; κ-CN, κ-casein; β-Lg, β-lactoglobulin; α-La, α-lactalbumin; n.d, not detected. Data are from Bellioni-Businco et al. (1999); Uniacke-Lowe et al. (2010); Hazebrouck et al. (2014); Lajnaf et al. (2022a).

3.3.2. Sheep's milk

The worldwide production of sheep (*Ovis aries*) milk is estimated to be 10.6 million tons per year representing 1.14% of total all mammalian milk production according to FAO Statistics (FAOSTAT, 2021).

Concerning its nutritional characteristics, sheep's milk has the highest content of fats (~6.4%, w/w) of all mammalian milk except buffalo milk that has more lipids than ovine milk. This fraction is characterised by the dominance of saturated fatty acids representing 75% of total fat fraction in sheep's milk, which is comparable with cow's and goat's milk. Furthermore, sheep's milk has also higher lactose and mineral contents than those in human,

Table 5
Immunogenicity of mammalian milk in cow's milk protein allergy (CMPA) and selective mammalian milk allergy (SMMA).

CMPA/SMMA	Methodology	Sample population	Results and conclusion	Reference
Goat milk				
CMPA	Cross reactivity study of IgE against bovine whey proteins (α-lactalbumin, β-lactoglobulin and serum albumin) and goat milk proteins.	Cow milk allergic patients n = 21: 12 children (7–80 months), eight children (1–60 months) and one adult	In vitro cross-reactivity between cow and goat milk proteins: anti-cow milk IgEs reacted completely with goat milk proteins.	Gjesing et al. (1986)
CMPA	In vitro and in vivo investigations: – skin tests with caprine and bovine milk, – detection of specific serum IgE to caprine and bovine milk – double-blind, placebo-controlled, oral food challenges with caprine and bovine milk.	Children with IgE-mediated CMPA: n = 26: 17 boys and 9 girls, aged 5 months to 7 years (median age, 2 years and 9 months).	– Positive skin test responses for all children – Positive double-blind placebo test to fresh goat milk for 92% of allergic children.	Bellioni-Businco et al. (1999)
CMPA	Cross reactivity study of IgE against bovine caseins to caseins of goat milk: specific IgE recognition of bovine proteins to caprine caseins.	58 children with CMPA with a sensitivity to bovine caseins: median age 11 months	93% of allergic patients to bovine caseins were also sensitive to caseins from goat milk.	Bernard et al. (1998)
SMMA	Skin prick tests with caprine milk and cheese as well as bovine milk, caseins and α-lactalbumin. Immunoblotting assays with inhibition to serum specific IgE and different goat and cow milk protein fractions.	27 year-old female patient (symptoms started at 24 years of age with two episodes of urticaria after ingestion of goat cheese).	Positive skin tests to goat milk and cheese and negative to cow milk. The appearance of IgE-binding 14 kDa band within immunoblot analysis that was totally inhibited after serum pre-incubation with goat milk.	Tavares et al. (2007)
Sheep milk				
CMPA	Cross reactivity between cow and sheep milk: studies used immuno-electrophoresis (SDS-PAGE and immunoblotting) and animal monoclonal antibodies (anti-mouse IgG antibodies).	Not determined	A strong recognition of cow milk protein monoclonal antibodies to the main part of ovine and caprine milk proteins.	Restani et al. (2002)
CMPA	The evaluation of Immunogenicity, sensitising capacity and cross-reactivity by ELISA.	17 children with CMPA, from 59 children with atopy but without food allergy, and from 27 healthy children without atopic disease.	In vitro cross-reactivity between α-casein from cow, sheep and goat milk: A strong recognition of anti-cow milk IgEs to caprine and ovine α-caseins.	Spuergin et al. (1997)
CMPA	The evaluation of the allergenicity of different mammalian milk substitutes in healthy subjects through ELISA analysis in order to measure IgE and IgG antibodies against cow, goat, sheep, camel and human milk.	Five hundred sera from a healthy population aged 18–65. Among these healthy individuals, 24 are considered as CMPA patients.	The immune reactivities of IgE, IgG and IgA to goat and sheep milk is very high. For individuals allergic to cow milk, the most allergenic alternatives to cow milk are sheep and goat milk compared with human and camel milk.	Vojdani et al. (2018)
CMPA	Test of the cross-reactivity between cow and sheep milk though the radio-allergo-sorbent test (RAST) and RAST inhibition on serum from patients with CMPA.	16 patients with CMPA: 15 children with an age from 7–5 months to 1–36 years (mean 6 years) with 10 males and five females and only one adult patient (a female aged 24 years).	Positive immunological reactions to sheep milk proteins for over than 90% of the studied CMPA patients sheep milk is the least suitable alternative for children with CMPA among milk from all mammalian species.	Dean et al. (1993)
CMPA and SMMA	In vitro and in vivo investigations: – skin tests – detection of specific serum IgE – ELISA analysis	CMPA allergic patients (n = 58) who successfully underwent cow milk oral immunotherapy.	Specific IgE to bovine caseins, goat whole milk, and sheep whole milk was 6.6, 6.5, and 6.5 kU L^{-1}. High prevalence of allergy to caprine and ovine milk (26%) in patients with CMPA due to the high homology between proteins of cow, goat and sheep milk. Limited cross-reactivity (up to 77.2%) between bovine, caprine and ovine caseins in the group of allergic patients to sheep and goat milk in contrast with almost 100% inhibition in patients with CMPA.	Rodriguez del Rio et al. (2012)
SMMA	Two-dimensional SDS PAGE and immunoblotting using extracts of sheep and cow milk and serum from two patients.	Two children of sheep milk allergy: – Subject 1:10-year-old boy – Subject 2: 15- year-old boy	– For subject 1 (with sheep milk allergy without CMPA): Positive IgE-ELISA results for sheep milk (~29.2 kU L^{-1}) and undetectable for cow milk (<0.35 kU L^{-1}).	Pazheri et al. (2014)

Table 5 (*continued*)

CMPA/SMMA	Methodology	Sample population	Results and conclusion	Reference
			– For subject 2 (with cow milk and sheep milk allergies): high IgE-ELISA for both of bovine (~34.1 kU L^{-1}) and ovine (~48.9 kU L^{-1}) milk.	
SMMA	Prick-to-prick skin testing	– Twin girls with disparate food allergy. Twin A developed allergies induced by goat and sheep milk. – Twin B has not yet manifested any food allergy.	– For twin A: high specific IgE level to sheep milk (57.7 kU L^{-1}) but not to cow milk (0.35 kU L^{-1}) with positive skin test results to sheep milk. – For twin B: negative skin test results.	Maskatia and Davis (2013)
Donkey milk				
CMPA	Feeding children with CMPA by donkey milk (250 mL kg^{-1} day^{-1}) supplemented with medium chain triglycerides (40 mL L^{-1} milk).	Nine infants (0–3 months) with multiple food hypersensitivity and severe symptoms of cow milk allergy including diarrhoea, abdominal pain, vomiting and growth retardation.	Tolerance of all allergic children (n = 9) to donkey milk and their provision by nutritional needs for normal growth with a weight increase of 39.8 g day^{-1}.	Iacono et al. (1992)
CMPA	A daily treatment of allergic children with a donkey milk-based diet (210–250 mL kg^{-1} day^{-1}) supplemented with medium chain triglycerides at a daily dose of 40 mL/L of milk.	21 children with CMPA (2–3 months) which are also intolerant to Hydrolysed cow milk proteins.	Clinical tolerance and negative results for 86% of patients with CMPA. Intolerance to donkey milk for 3/21 of patients with different symptoms vomiting (one case) or diarrhoea (two cases).	Carroccio et al. (2000)
CMPA	Donkey milk -based diet (200 –500 mL day^{-1}) of allergic children depending on age	46 children with CMPA (1–146 months)	Clinical tolerance of donkey milk for thirty-eight children with CMPA (82.6%) hypersensitivity to donkey milk for the remaining eight children (17.4%)	Monti et al. (2007)
CMPA	Diets of donkey milk to children with CMPA.	92 children with CMPA (7.5–12.5 months).	Clinical tolerance and improvement in the nutritional parameters for 83 children (90.2%): 20 to 23 out of 92 children with non-IgE-mediated CMPA and 63 out of 69 children with IgE-mediated allergy.	Monti et al. (2012)
SMMA	In vivo and in vitro tests: skin prick tests with milk protein fractions α-lactalbumin, β-lactoglobulin, and casein prick-by-prick tests with cow and donkey milk. Basophil activation test (BAT) with cow and donkey milk.	A 25-year-old woman with no history of food allergy and tolerated cow milk.	Positive skin test responses for donkey milk and a negative reaction with cow milk protein fractions (caseins, β-lactoglobulin and α-lactalbumin). Positive results of basophil activation test (BAT) for donkey milk and negative results for cow milk.	Giorgis et al. (2018).
SMMA	Skin prick tests and patch tests with cow and donkey milk under medical supervision	A 25-year-old woman with a history of personal atopic dermatitis and allergic asthma.	Positive skin prick tests for donkey milk and negative reaction for cow milk. Positive patch tests with donkey milk.	Peeters et al. (2017)
Mare milk				
CMPA	Skin prick tests for allergic children with cow and mare milk and double-blind placebo-controlled oral food challenge with fresh cow milk and fresh mare milk. In vitro analysis using the sera of allergic children and proteins of mare milk.	Twenty-five children (17 male and 8 female) aged 19–72 months (median age 34 months) with IgE-mediated CMPA.	Positive skin test responses Two children out of twenty-five (characterised by a severe IgE-mediated CMPA) Positive oral food challenges to mare milk for only one child A weak recognition for proteins of mare milk by IgE from the sera of allergic patients to cow milk.	Businco et al. (2000)
CMPA	Skin prick tests allergic childrenwith cow and mare milk. Double blind placebo controlled oral food challenge with cow and mare milk and, as placebo, a soy formula.	25 CMPA children, with a median age of 34 months.	Negative skin test responses for 96% of children. Positive challenge test for only one patient. Mare milk can be regarded as a suitable alternative for children with IgE-mediated CMPA.	Curadi and Giampietro (2001).
SMMA	Prick tests with the cream containing mare milk. Measurement of specific IgE in the patient's serum using radio-allergosorbent tests.	45-year-old women showing allergy to sheep milk but with no concomitant CMPA.	Positive Prick test reaction High specific IgE level to mare milk (>100 kU L^{-1}).	Verhulst et al. (2016).
Camel milk				
CMPA	Studies used immuno-electrophoresis (SDS-PAGE and immunoblotting) and animal monoclonal antibodies (anti-mouse IgG antibodies).	Not determined	Absence of cross-reactivity between bovine and camel proteins Absence of reaction between the animal anti-bovine monoclonal antibodies and proteins from camel proteins.	Restani et al. (2002)

(*continued on next page*)

Table 5 (*continued*)

CMPA/SMMA	Methodology	Sample population	Results and conclusion	Reference
CMPA	In vitro investigation: immunoblotting by using sera from allergic children to cow and sheep milk towards monoclonal antibodies specific for bovine proteins (caseins and β-lactoglobulin) to detect antibody−antigen complexes	Six children allergic to cow milk (four males and two females) and one child with sheep milk allergy.	Absence of recognition by IgEs from children allergic to cow and sheep milk to camel milk proteins.	Restani et al. (1999)
CMPA	Immunoblotting and enzyme-linked immunosorbent assay (ELISA) tests using sera from allergic children.	Children with CMPA (n = 40) aged 6 months to 8 years.	Absence of immunological cross-reactivity between proteins from cow and camel milk including both of caseins and whey proteins	El-Agamy et al. (2009)
CMPA	The allergenicity and immunogenicity tests of camel and bovine caseins and whey proteins using animal models (Brown Norway rat model). The evaluation of Immunogenicity, sensitising capacity and cross-reactivity by ELISA.	Not determined	Low cross-reactivity of cow and camel milk due to the low protein similarity between both milk types leading to recommend camel milk as a new protein source to children with CMPA.	Maryniak et al. (2018)
CMPA	Crossed clinical trial for the use of camel milk versus amino acid formula by the ingestion of camel milk to allergic children with CMPA	49 allergic children with CMPA between one and 18 years of age with diagnosed CMPA.	Tolerability of camel milk for CMPA patients at the age of one year and above leading to consider it as a suitable alternative with a good flavour and taste in dairy formulas.	Navarrete-Rodríguez et al. (2018)
SMMA	Skin prick tests with cow and camel milk.	6-year-old boy with anaphylaxis to camel milk proteins and with no CMPA.	Positive skin prick tests responses for camel milk and negative responses for cow milk.	Al-Hammadi et al. (2010)

bovine and caprine milk (Muehlhoff, Bennett, & McMahon, 2013; Verduci et al., 2019).

Sheep's milk is also the richest milk of proteins with an average protein' content of 5.6% (w/w). Similarly to goat's milk, β-casein is the main protein fraction in sheep's milk reaching a concentration of 28.0 g L^{-1} (Table 3). This milk has also higher amounts of α_{S2}-casein, κ-casein, β-lactoglobulin and α-lactalbumin and lower amounts of α_{S1}-casein than those in cow's milk. Ovine β-lactoglobulin is the major whey protein of sheep's milk with an almost double quantity in comparison with cow's milk (up to 7.2 g L^{-1}) (Nayak et al., 2020; Park, Juárez, Ramos, & Haenlein, 2007; Wendorff & Haenlein, 2017).

Sheep's milk is very popular for some populations due to its nutritional value, special taste and high fat content cheeses. Currently, these dairy products are essential for populations in regions that are not suitable for goats and cows. They are also considered as a potential alternative for people with CMPA (van den Brom, de Jong, van Engelen, Heuvelink, & Vellema, 2020). However, similarly to goat's milk, previous research did not recommend this substitution because of the high sequence identity levels between proteins of cow's and sheep's milk (higher than 80%, Table 4). For instance, ovine β-casein is characterised by the highest identity rates with its bovine counterpart compared with goat, donkey, mare and camel β-caseins (~91.4% of sequence identity with bovine β-casein) (Table 4). Similarly, whey proteins in sheep's milk are very similar to their bovine counterparts: ovine β-lactoglobulin and α-lactalbumin show 95.7% and 96.7% sequence identity rates, respectively (Table 4).

The immuno-electrophoresis analysis undertaken by Restani, Beretta, Fiocchi, Ballabio, and Galli (2002) showed that specific cow's milk proteins' monoclonal antibodies are able to recognise the main part of ovine and caprine milk proteins, whereas a weak cross-reactivity was detected for milk proteins from donkeys and mares (Table 5). In the same way, several in vivo studies showed that 98% of allergic children with a mean age of 6 years to bovine caseins (n = 26) were simultaneously allergic to ovine caseins (Dean, Adler, Ruge, & Warner, 1993; Høst & Halken, 2014).

Furthermore, an in vitro cross-reactivity between α-caseins from cow's and sheep's milk was reported by Spuergin et al. (1997). These authors noted that ovine and caprine α-casein were mostly recognised by IgE antibodies from the sera of children with CMPA (n = 17). Thus, α-caseins from ovine and caprine milk share epitopes with their bovine counterpart, which is probably the main cause of cross reaction between sheep's, goat's and cow's milk. Vojdani, Turnpaugh, and Vojdani (2018) reported also that, the most allergenic alternatives to cow's milk for individuals who are allergic to this milk (n = 24) are sheep's and goat's milk compared with human's and camel's milk as well as plant-based drink including almond and soy based substituted. Before choosing an alternative for cow's milk, quantitative blood testing for determination of IgE, IgG and IgA antibodies against different substitutes revealed also that the immune reactivities of IgE, IgG and IgA to ovine and caprine milk is very high in all allergic and not allergic individuals to sheep's and goat's milk (n = 500).

However, almost all of cow's milk-allergic patients who have acquired tolerance to cow's milk proteins could tolerate caprine and ovine milk proteins as well without nutritional risk of allergies as reported by Nachshon et al. (2020). Consequently, the majority of researches reported that sheep's milk is unsuitable for infant feeding because of its high immunological cross-reactivity of sheep's milk and its nutritional composition (Dean et al., 1993; Dhesi et al., 2020; Restani et al., 1999, 2002).

Sheep's milk has been shown to cause allergic reactions in cow's milk allergic patients, probably due to the high homology of goat's and sheep's milk proteins with cow's milk proteins. Rodriguez del Rio et al. (2012) reported a prevalence of 26% of allergy to either goat's milk or sheep's milk or to both in a population of children who were successfully treated with cow's milk oral immunotherapy, with 47% of positive oral food challenges to goat's and sheep's milk, leading to anaphylactic reactions. Furthermore, limited cross-reactivity (up to 77.2%) between cow's milk casein and caprine and ovine caseins in the group of allergic patients to sheep's and goat's milk in contrast with almost 100% inhibition in

patients with CMPA (Hazebrouck et al., 2014; Rodriguez del Rio et al., 2012).

Sheep's milk and cheeses are able to induce alone a specific allergy that is not associated with that of cow's milk proteins. This allergy is unusual and rare of which only few cases have been detected in the world (El-Agamy, 2007). A case study was proposed by Pazheri, Melton, Poptic, and Willard (2014) in which they used two children of sheep's milk allergy (who already experienced anaphylactic reactions to two sheep's milk cheeses: Romano and Ricotta cheeses), one with concomitant CMPA and the other without CMPA. For the child with sheep's milk allergy without CMPA, IgE-ELISA was positive for sheep's milk (~29.2 kU L^{-1}) and undetectable for cow's milk (<0.35 kU L^{-1}). Consequently, this patient could consume dairy products without cross-allergenicity between bovine and ovine milk. However, IgE-ELISA was significantly high including both of cow's (~34.1 kU L^{-1}) and sheep's (~48.9 kU L^{-1}) milk for the child with cow's milk and sheep's milk allergies. Another example of sheep's and goat's milk allergies was described by Maskatia and Davis (2013). In this case, identical twin girls with goat's and sheep's milk allergy without cow's milk allergy experienced anaphylactic reactions. The development of these unusual allergies could be partially explained by stressful prenatal period with impaired placental blood flow in utero (Maskatia & Davis, 2013).

3.3.3. *Donkey's milk*

Donkey (*Equus asinus*) milk has been used in various regions in the world, particularly as a treatment for a series of diseases such as bronchitis, asthma, wound healing, gastritis and joint pain. The production of this milk is limited when compared with other species: it is accounted for less than 0.1% of total milk production without any other world-specific statistics (Conte & Panebianco, 2019; Derdak et al., 2020).

Nutritionally, the donkey's milk is comparable with human's milk, as it contains similar basic chemical compositions. It is distinguished by a particular physico-chemical composition similar to that of human's milk. First, donkey's milk contains the lowest amounts of fats than those in other milk species with consequent lower energy content (~39.68 kcal). However, fat fraction of donkey's milk is characterised by a better nutritional quality than that of cow's milk, despite its low content. For instance, fat fraction in donkey's milk contains higher levels of poly-unsaturated fatty acids and lower levels of saturated fatty acids than those of cow's milk. It contains also linoleic-acid and α-linolenic acid that are essential fatty acids and precursors of arachidonic acid and docosahexaenoic acid (DHA, C22:6), respectively (Muehlhoff et al., 2013; Nayak et al., 2020; Verduci et al., 2019). The lactose content in donkey's milk is the highest among other mammalian milk (~6.3%, w/w) leading to a better palatability and an easier intestinal absorption of calcium (Dugo et al., 2005; Nayak et al., 2020). Nevertheless, this milk is poorer in mineral salts when compared with cow's milk (~0.7% and 0.4%, w/w, for cow's and donkey's milk, respectively).

As human's milk, donkey's milk has the lowest amounts of protein (~1.91%, w/w) among all milk species. Donkey's milk has also the lowest casein/whey protein ratio among milk of all mammalian species except human's milk (47.28% of caseins and 36.96% of whey proteins) (Nayak et al., 2020). The β-casein and β-lactoglobulin are the main protein fractions in donkey's milk with concentrations of 3.9 and 3.7 g L^{-1}, respectively. Considerable amounts of α-lactalbumin were also reported in donkey's milk reaching a value of 3.0 g L^{-1} (Table 3). Similarly to human's milk, donkey's milk contains lower amounts of α_{S1}-casein (Bos d9) and α_{S2}-casein (Bos d10) than to those in cow's milk with a concentration ranging between 0.2 and 2.0 g L^{-1} (Table 3). Furthermore, κ-casein (Bos d12) was totally absent donkey's milk in contrast to the other milk (Hinz et al., 2012). These findings suggest the possible use of this milk as a potential alternative to children with CMPA despite the dominance of the β-lactoglobulin (Bos d5) and α-lactalbumin (Bos d4) in donkey's milk (Derdak et al., 2020). In addition to the particular protein composition, donkey's milk proteins display relatively low sequence identity levels with their bovine homologues varying between 39.0% (α_{S1}-casein, Bos d9) and 56.2% (β-lactoglobulin, Bos d5), except for α-lactalbumin, i.e., Bos d4 which shows an identity level of ~71.5% (Table 4).

Various researchers have evaluated donkey's milk as a new alternative for infants with CMPA considering its high palatability, similar protein composition to that of humans' milk and the low sequence identity rates with bovine milk proteins (Garhwal et al., 2022; Keipopele, Seifu, & Sekwati-Monang, 2018; Papademas, Mousikos, & Aspri, 2022).

Donkey's milk is characterised by a reduced allergenicity and high tolerability by children with CMPA. Therefore, donkey's milk can be successfully used for children suffering from both of IgE- and non-IgE-mediated CMPA with an adequate increase in length, stature, and body mass index of children after consumption of donkey's milk for several months. However, the inclusion of this milk in the diet of consumers with CMPA should be supervised by a nutritionist as donkey's milk proteins can cross-react with cow's milk proteins (Table 5) (Martini, Altomonte, Tricò, Lapenta, & Salari, 2021; Papademas et al., 2022).

Immunochemical analysis revealed that caseins of donkey's milk are weakly recognised by IgE from allergic patients to cow's milk. Previous in vivo studies revealed also that two out of 23 patients with CMPA (8.7%) exhibited allergic reactions for both bovine and donkey whey proteins (Souroullas et al., 2018).

Clinical studies on the effect of donkey's milk in the treatment of CMPA in children were in great consistence with in vitro analysis of previous work revealing high tolerability of this milk by infants suffering from CMPA (Table 5). Overall, clinical studies illustrated that donkey's milk is well tolerated (82.6–88%) by infants (Souroullas et al., 2018).

Carroccio et al. (2000) studied a group of 21 children aged 2–3 months with symptoms related to CMPA and who were also intolerant to hydrolysed cow's milk proteins; all patients underwent daily treatment of allergic children with a donkey's milk based diet (210–250 mL kg^{-1} day^{-1}) supplemented with medium chain triglycerides at a daily dose of 40 mL L^{-1} of milk. Therefore, 86% of 21 patients with CMPA showed a clinical tolerance and negative results through immunological assays using radio-allergosorbent test (RAST). In the same way, Monti et al. (2007) proved the palatability and adequacy of donkey's milk to children with CMPA through a simple trial administered donkey's milk to a group of 46 children (aged 1–146 months) with CMPA. Indeed, thirty-eight children with CMPA (82.6%) liked and tolerated this milk after an ingestion of 200–500 mL per day, whereas the remaining eight children (17.4%) showed hypersensitivity to this milk (Table 3). Another study revealed that donkey's milk was well tolerated for 90.2% of children with CMPA (aged 7.5–12.5 months) with severe IgE-mediated CMPA (n = 92). For five patients who already experienced anaphylactic reactions to cow's milk, four presented a positive reaction to donkey's milk by oral challenge-test. Clinical studies showed that donkey's milk was well tolerated by 20–23 out of 92 children with non-IgE-mediated CMPA and 63 out of 69 children with IgE-mediated allergy. Furthermore, all children showed an improvement of their weight and height (Monti et al., 2012). A simple trial study with the participation of nine children aged 0–3 months with multiple allergies against bovine milk proteins was assessed to evaluate the consumption effect of donkey's milk and its tolerability. Donkey's milk (250 mL kg^{-1} day^{-1}) which was supplemented with medium chain triglycerides (40 mL L^{-1} of milk) was well-tolerated by all allergic children

(n = 9) and provided nutritional needs for normal growth with a weight increase of 39.8 g day^{-1} (Iacono et al., 1992).

In addition to its high tolerability by CMPA infants, the consumption of donkey's milk is associated with various health benefits as reported by many clinical studies. For instance, Monti et al. (2007) found that 52% of children with CMPA became cow's milk tolerant during the period of study. A significant improvement in clinical symptoms for children with atopic dermatitis and CMPA was observed after the ingestion of donkey's milk. On the contrary, these symptoms worsened after goat's milk consumption (Vita et al., 2007).

Due to its hypoallergenic properties, donkey's milk has proved to be a suitable alternative in feeding children affected by CMPA through immunochemical analysis and clinical studies. The tolerability and the low allergenicity of donkey's milk to children with CMPA is obviously related to its protein fraction (Bertino et al., 2010). The studies on donkey's milk clearly demonstrate that the proteins of this milk are more closely related with the human homologues rather than cow's milk counterparts (Barłowska et al., 2011). Moreover, the low allergenic properties of donkey's milk would seem to be related to the low total protein content as well as the low ratio of caseins to whey fraction. The presence of multiple amino acid composition differences in almost all IgE-binding linear epitopes in cow's milk proteins with respect to the corresponding regions of their counterparts in donkey's milk can contribute to its hypoallergenicity (Bertino et al., 2010; Souroullas et al., 2018; Uniacke-Lowe, Huppertz, & Fox, 2010).

However, clinical studies showed that donkey's milk did not achieve the minimum required 90% tolerability that will allow classification of this milk as hypoallergenic formulas to infants with CMPA. This behaviour can be explained by the relative high concentrations of β-lactoglobulin (Bos d5) in donkey's milk. Furthermore, α-lactalbumin (Bos d4) is highly similar to its bovine counterpart, leading to suggest it as the main responsible allergen for cross-reactivity between donkey's milk proteins and cow's milk proteins. The use of unmodified donkey's milk in a 5-month cow's milk allergic infant can result to a nutritional imbalance as iron deficiency and low weight caused by the lower caloric intake (D'Auria et al., 2011). Therefore, this milk may not be suitable as a complete replacer of infant formula, whereas it can act as a supplement to a balanced diet. Furthermore, further research is needed to validate the use of donkey's milk for children, especially under the age of one year, and to determine the cross reaction between bovine and equine α-lactalbumins.

As observed for goat's and sheep's milk, donkey's milk is also able to induce an allergy that is not associated with CMPA. This allergy is a rare clinical condition that was recently unveiled and reported (Giorgis et al., 2018; Peeters, Herman, & Baeck, 2017; Souroullas et al., 2018). An example of donkey's milk allergy was previously described by Giorgis et al. (2018). In this case, a patient with no history of food allergy developed respiratory allergy to donkey's milk characterised by both of asthma and rhinoconjunctivitis after handling it. Skin prick tests yielded a positive reaction with donkey's milk and a negative reaction with cow's milk protein fractions (caseins, β-lactoglobulin and α-lactalbumin) (Table 5). In the same way, the results of basophil activation test (BAT) were positive for donkey's milk and negative for cow's milk (Giorgis et al., 2018). Another example of donkey's milk allergy was reported by Peeters et al. (2017). In this case, the allergic patient who had a history of allergic asthma and atopic dermatitis showed a facial angioedema within 5 min after consuming donkey's milk. Thus, the appearance of this allergy was explained by the sensitisation of the patient through repeated skin contact with donkey's milk-based emollients leading to the development of an immediate hypersensitivity reaction to this milk (Peeters et al., 2017).

3.3.4. Mare's milk

Horse or mare (*Equus callabus*) milk is still consumed in Central Asia and Mongolia in different forms raw milk and fermented products. As donkey's milk, the production of mare's milk was estimated to be less than 0.1% of the total mammalian milk production, whereas no world specific statistics are available for this milk (Conte & Panebianco, 2019).

Donkeys and horses belong to the Equus family leading to a similar physico-chemical composition of donkey's and mare's milk including proteins, fats, mineral salt contents and lactose (Polidori, Ariani, & Vincenzetti, 2015; Verduci et al., 2019). Similarly to donkey's milk, mare's milk contains high levels of lactose (6.37%, w/w) and low levels of fats (1.21%, w/w), proteins (2.14%, w/w) and minerals (0.42%, w/w). The fat fraction of mare's milk contains trans fatty acids as well as conjugated linoleic acid (C18:2, cis-9, trans-11), whereas these compounds were totally absent in donkey's milk. On the other hand, mare's milk has higher vitamins amounts than those of donkey's milk, especially vitamin C whose quantity is ranged between 1287 and 8100 mg 100 g^{-1} (Muehlhoff et al., 2013; Nayak et al., 2020; Verduci et al., 2019).

Mare's milk is distinguished by the low caseins content that is similar to the whey proteins content. This milk has a comparable proteins composition with that of donkey's milk, except for β-casein and κ-casein whose quantities are significantly higher than those of donkey's milk (11.0 and 4.6 g L^{-1} for mare β-casein and κ-casein, respectively) (Table 3). Furthermore, the concentrations of α-lactalbumin and β-lactoglobulin are almost comparable in mare's milk (~3 g L^{-1}), differently from bovine milk (Table 3).

Some researches highlighted the possible use of mare's milk as milk alternative for children allergic to cow's milk (Table 5) (Businco et al., 2000; Curadi & Giampietro, 2001; Verhulst, Kerre, & Goossens, 2016). Mare's milk proteins show relatively lower sequence identity levels with cow's milk proteins when compared with those of donkey's milk proteins ranging between 38.2% (α_{S1}-casein, Bos d9) and 53.1% (β-casein and α_{S1}-casein), except for β-lactologbulin (Bos d5) and α-lactalbumin (Bos d4) and whose identity levels are respectively ~57.2 and 72.4% (Table 4).

By taking into account the high digestibility as well as the low caseins amounts and sequence identity levels of proteins, mare's milk has been proposed as a new alternative for infants with CMPA (Kondybayev, Loiseau, Achir, Mestres, & Konuspayeva, 2021). In vivo and in vitro tests of Businco et al. (2000) showed that mare's milk can be considered as a good substitute of bovine milk for children with severe IgE-mediated CMPA. Proteins of this milk are weakly recognised by IgE from the sera of allergic patients to cow's milk. Meanwhile, two children out of twenty-five characterised by a severe IgE-mediated CMPA had positive skin test responses and only one child had a positive oral food challenges to mare's milk, while all these allergic children presented strong positive skin test responses and oral food challenges to cow's milk (Businco et al., 2000). Another study revealed that mare's milk was tolerated for 96% of children with proven IgE-mediated CMPA (n = 25) through skin prick tests and only one patient presented positive challenge test. These findings suggested that this product can be regarded as a suitable alternative for children with IgE-mediated CMPA (Curadi & Giampietro, 2001).

Mare's milk proteins, especially α-lactalbumin and β-lactoglobulin are found to be able to induce an unusual and rare allergy which is not associated with that of cow's milk (Gall, Kalveram, Sick, & Sterry, 1996).

Selective allergies to mare's milk without concomitant CMPA have been reported. One case report described skin contact allergy after application of a body cream containing mare's milk proteins as an ingredient with manifestation of itchiness and swelling on the

face but also mare's milk α-lactalbumin-positive IgE in serum (>100 kU L^{-1}) (Verhulst et al., 2016).

3.3.5. Camel's milk

Camel (*Camelus dromedarius*) milk has an important role for nutrition of humans in arid parts and hot regions of the world (Al haj & Al Kanhal, 2010; Kappeler, Ackermann, Farah, & Puhan, 1999; Lajnaf, Trigui, Samet-Bali, Attia, & Ayadi, 2020). Recently, there has been a growing interest in this milk due to its high nutritional value and its exceptional therapeutic effects that are not comparable with any other milk (El-Agamy, 2009; Lajnaf et al., 2022a; Yadav, Kumar, Priyadarshini, & Singh, 2015a, Yadav et al., 2015b). Camel's milk production was estimated at 3.11 million tons per year representing 0.34% of the total milk production of the world according to the recent statistics by the Food and Agriculture Organisation (FAOSTAT, 2021).

Camel's milk was reported to provide various potential health benefits to the consumer including anti-carcinogenic hypocholesterolaemic, anti-diabetic, anti-autism and hypoallergenicity effects due to the due to the bioactive substances that are present there naturally (vitamins, and lactoferrin) (Hailu et al., 2016; Ho, Zou, & Bansal, 2021; Izadi et al., 2019). Camel's milk is beneficial for immune problems such as sclerosis and Crohn's infections as it boosts the immune system (Conesa et al., 2008; Shabo, Barzel, & Yagil, 2008; Sumaira, Solangi, Anwar, & Kalwar, 2020; Yadav et al., 2015a). Other studies have found that camel's milk also ameliorates alcoholic liver injury through its anti-apoptotic, anti-inflammatory and antioxidant substances (Badawy, El-Magd, & AlSadrah, 2018; Darwish, Raboh, & Mahdy, 2012; Uversky, El-Fakharany, Abu-Serie, Almehdar, & Redwan, 2017).

Nutritionally, camel's milk is reported to contain similar amounts of lactose and lipids than those in cow's milk (Nayak et al., 2020). However, this milk is distinguished by its high amount in vitamin B3 (niacin) and vitamin C whose concentration is five times higher than that of cow's milk (24–52 mg L^{-1}) as well as various minerals including calcium, magnesium, potassium, phosphorus and sodium (Al haj & Al Kanhal, 2010).

Proteins levels in camel's milk are usually between 2.5% and 4.9% (w/w) depending on the breed and seasonal conditions (Al haj & Al Kanhal, 2010). Camel's milk is the only mammalian milk with deficiency of β-lactoglobulin (Bos d5) as observed for human's milk (Lajnaf et al., 2020; 2022c). Hence, α-lactalbumin (Bos d4) is the most common whey protein with a concentration of 3.5 g L^{-1} and representing 72.8% of total camel whey proteins (Table 3) (Lajnaf et al., 2018). The β-casein (Bos d11) is the main protein fraction in camel's milk with a concentration of 15.0 g L^{-1} (Table 3) representing 44% of total camel milk proteins (Lajnaf et al., 2020). Camel's milk lacks of α_{S2}-casein (Bos d10) and κ-casein (Bos d12) conferring its greater digestibility and lower incidence of allergies when compared with bovine milk (Izadi et al., 2019).

In addition to the particular proteins composition of camel's milk, camel proteins show relatively low sequence identity levels with cow's milk proteins (less than 53%) ranging between 40.5% (α_{S1}-casein, Bos d9) and 53.5% (κ-casein, Bos d12), except for β-casein (Bos d11) and α-lactalbumin (Bos d4) and whose identity levels are respectively 63.8% and 69.1% (Table 4). These features lead to suggest the possible use of camel's milk as an alternative to children with CMPA (El-Agamy, Nawar, Shamsia, Awad, & Haenlein, 2009; Ho et al., 2021; Izadi et al., 2019; Verduci et al., 2019).

A few studies about the allergenicity of camel's milk proteins have been carried out. The in vitro studies of Restani et al. (2002) revealed that cross-reactivity between bovine and camel proteins was not observed and none of the animal anti-bovine monoclonal antibodies reacted with proteins from camel proteins. Furthermore, no anti-β-lactoglobulin antibody reacted with camel's milk proteins as it is devoid of β-lactoglobulin. Both in vivo and in vitro studies showed that IgEs from children allergic with CMPA (n = 6) are able to recognise the most parts of milk proteins from goat, sheep and buffalo, while no camel's milk (Restani et al., 1999). Camel's milk proteins were not recognised by IgEs from a child allergic to sheep's milk suggesting that camel's milk seems to be an interesting alternative for children with CMPA and allergy caused by sheep's milk (Restani et al., 1999, 2002). Results obtained from the in vitro ELISA inhibition tests using sera from allergic children (n = 40) showed the absence of immunological cross-reactivity between proteins from bovine and camel milk including both of caseins and whey proteins (El-Agamy et al., 2009) (Table 5).

Further in vivo investigations involving animal models (Brown Norway rat modal) noted that camel and bovine milk have low cross-reactivity due to the low protein similarity between both milk (Maryniak, Hansen, Ballegaard, Sancho, & Bøgh, 2018). Findings demonstrate that camel's milk could be strongly recommended as a new protein source for the nutrition of children with CMPA. Navarrete-Rodríguez et al. (2018) have also implemented a cross-over clinical study to determine the tolerability and safety of camel's milk ingestion for 49 allergic children with CMPA. Thus, these authors reported that camel's milk is tolerable and safe for patients at the age of one year and above and can be considered as a suitable alternative with a good flavour and taste in dairy formulas.

As milk from other ruminants and equines, camel's milk is able to induce sensitisation (Table 5). Indeed, an atopic child with anaphylaxis to camel's milk proteins and with no CMPA has been reported in the United Arab Emirates (Al-Hammadi, El-Hassan, & Al-Reyami, 2010). Camel's milk allergy has been reported to be a distinct and very rare disease entity, whose clinical manifestations are mainly systemic and cutaneous allergic reactions. Risk factors are concomitant other allergies such as CMPA, atopic dermatitis and early life exposure to camel's milk (Ehlayel & Bener, 2018).

Finally, based on previous findings, camel's milk seems to be a suitable and tolerable alternative to children with CMPA. However, further in vivo and in vitro investigations are required to validate the use of the proteins of this milk especially the α-lactalbumin and the β-casein whose identity levels with cow's milk proteins are the highest among other camel's milk proteins (>63%, Table 4). For instance, sequences alignment of between the β-caseins from cow's and camel's milk reveals the presence of 4 domains of 8 continuous identical amino-acids which could induce a significant risk of cross-reaction.

4. Conclusion and future trends

Despite their worldwide consumption and production, cow's milk and dairy products are among the most common food allergens. Hence, CMPA is the first most common food allergies responsible for anaphylaxis reactions in young children. In this review, we provided an overview of current and potential future cow's milk alternatives for children with CMPA that would be of great interest to researchers and food industrials.

Overall, hydrolysed cow's milk formulas including EHF and AAF as well as plant-based formulas, especially rice-based formulas, are suggested to be a good first-line alternative. Milk from other mammalian species including goat's, sheep's, donkey's, mare's and camel's milk are also suggested as potential alternatives for children with severe CMPA after the age of one year. However, milk proteins from different mammalian species may present the risk of high risk cross-reactivity with cow's milk proteins as they share similar parts of their amino acid sequences with their bovine counterparts, which makes them similar in their capacity to bind specific antibodies. The use of goat's and sheep's milk is not recommended because of strong cross-reaction between caprine and

ovine proteins with cow's milk proteins. On the other hand, camel's, donkey's and mare's milk, which are used in popular practice for children in CMPA, are promising alternative protein sources. Proteins in camel's, donkey's and mare's milk show low sequence identity levels and hence, weak cross-reaction through in vivo and in vitro studies. Camel's milk, which lacks the protein β-lactoglobulin, would have the potential to be used especially for children who are allergic to the main milk allergen β-lactoglobulin (Bos d5). Thus, new hypoallergenic formulas can be manufactured using camel's milk for children who are allergenic to this allergen. It should be noted that calorific inadequacy and the low lipid and iron contents in equine milk must be covered by either fortification with unsaturated fatty acids or by consumption as part of a balanced diet. Therefore, equine milk may not be suitable as a complete replacer of hypoallergenic formula, but it can act as a supplement to a balanced diet; camel's milk has been suggested as a suitable alternative due to its differences from cow's milk proteins as well as its high nutritional contents.

The results about camel's milk are still too preliminary and further in vivo and in vitro investigations are required to validate the use of camel's milk proteins, particularly α-lactalbumin and β-casein that are characterised by a relative high sequence identity levels. These future investigations should provide valuable support for the development cow's milk substitute for children with CMPA.

Declaration of competing interest

None.

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