COW'S MILK PROTEIN ALLERGY AND ALTERNATIVE MILKS

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Abstract

Allergy is a hypersensitive response of the immune system to substances that enter or come into contact with the body. Recently, food allergies are quite common. Food allergy is defined as abnormal rapid immunological reactions of normally beneficial food components (usually proteins). Milk protein allergies are one of them and can cause diseases such as obesity, type 2 diabetes, and cardiovascular diseases.

Cow's milk protein allergy (CMPA) is very common in infants, and this type of allergy is the immune system's response to milk proteins. It has been determined that infants are sensitive to at least twenty or more protein contents in cow's milk. Cow's milk proteins consist of approximately 80% casein and 20% serum proteins composed of α-lactalbumin (α-LA), serum albumin, β-lactoglobulin (β-LG), proteose-peptones and immunoglobulins, and other small protein fractions. Milk protein allergy (MPA) is caused by casein, β-LG, and α-LA fractions. Hypersensitivity to casein fractions has been reported in studies on casein, the main protein of milk. β-LG, which contains a high percentage of essential amino acids, constitutes 50% of the serum proteins in cow's milk. The absence of this protein in breast milk suggests that it may be the cause of allergic reactions.

CMPA negatively affects the growth and adequate nutrition of infants. Therefore, CMPA is an important issue that needs to be resolved. Technological processes such as enzymatic hydrolysis, high-pressure applications, and heat-applied filtration can be used to reduce protein allergy. If these applications are used in cow's milk, it is thought that it will be a good alternative to breast milk by eliminating the negative effects of proteins that cause food allergies. Another alternative method is to use milk obtained from other animals. In this context, the first milk that comes to mind is goat milk or camel milk. It is known that the main source of cow's milk allergy is β-LG and αs1-casein proteins. The basic proteins of goat, sheep, camel, and donkey milk are the same as cow's milk. On the other hand, goat milk's digestibility increases as it contains less casein protein and more serum protein than cow's milk. In addition, goat milk is richer in essential amino acids and the amount of αs1-casein in it is very low. Therefore, its allergic feature is different from cow's milk. Camel milk is rich in whey proteins lactoferrin, immunoglobulins, lysozyme, α-LA, and serum albumin and contains less β-LG. This shows that it can be a good alternative to CMPA.

Vegetable milks, which have become very popular among consumers, especially vegetarians and vegans in recent years, are also an alternative to cow's milk against CMPA. Because these non-dairy products are natural and healthy, they are considered the best nutritional choice. In addition to being protected from diseases such as CMPA, lactose intolerance, coronary heart diseases and hypercholesterolemia, the fact that they contain more minerals, dietary fibres and the bioavailability of the vitamin has led to an increase in the consumption of these products. The most known and consumed plant-based milks are produced from soy, almond, rice, and coconut.

Keywords: Milk allergy, protein, casein, whey protein

I. INTRODUCTION

Milk is a liquid secreted by more than 4000 species of female mammals to feed the newborn baby and meet its basic needs [1, 2]. Milk, which has a very important function in human nutrition, is a good source of all nutrients except iron and vitamin C. It is a very important food source for bone health, especially in old age, infancy, and pregnancy-breastfeeding. Cow's milk and its products are highly nutritious and valuable because of the high-quality proteins, essential amino acids, minerals, and vitamins they contain, as well as immune functions [3]. Numerous studies have been conducted on the relationship of chronic diseases such as hypertension, obesity, and cancer with milk [4, 5, 6]. Milk contains 5.3 g/kg nitrogen, 95% of which is in the form of protein; Apart from that, it contains hundreds of minor components such as aroma compounds, vitamins, and metal ions [2, 6]. Cow's milk proteins are generally classified into two main groups, considering their solubility, rheological properties, and functionality: casein and serum proteins. Casein proteins consist of αs1- αs2-, β-, and κ-casein fractions, while whey proteins consist of α-LA, β-LG, lactotransferrin, and imimmunoglobulins. Apart from these, proteose-peptone fractions are also included in whey proteins [2, 7].

Casein, the main protein of cow's milk, can be obtained by coagulating the milk with enzymes or acid (at pH 4.6) or by ultracentrifugation. Because they have a primary protein structure, they are resistant to heat treatments but sensitive to proteolytic enzymes [3]. The size of casein and its micelles vary according to many factors such as protein concentration, pH, ion resistance, and temperature [2, 7, 8].

On the other hand, serum proteins, the second protein of milk, are highly structured proteins with a secondary and tertiary protein structure. Globular serum proteins are relatively resistant to proteolytic enzymes but very sensitive to heat. Due to the disulfide bridges and free sulfhydryl groups in their structure, they are easily denatured by heat treatments. β-LG, which constitutes 50% of serum proteins, is not found in breast milk. Comparing 25% of serum proteins, α-LA has a high homology sequence compared to human milk. Other proteins, such as immunoglobulins, blood serum albumin, and lactoferrins, which make up serum proteins, come from the blood [3].

The composition of cow's milk varies depending on factors such as the animal's nutrition, age, number of lactations, genetic factors, climate, seasons, number of milkings, and udder diseases. Cow's milk is consumed much more than other milks due to its high nutritional value and high yield. However, cow's milk is different in composition and nutritionally from human milk. The amount of protein in cow's milk (3.4%) is approximately twice the amount of protein in breast milk (0.9-1.9%). In addition, β-LG and α $-S_1$ casein differences are not found in breast milk. On the other hand, the composition of breast milk is closer to horse and donkey milk (Table 1).

The high ratio of casein and serum proteins in cow's milk makes it perfect for producing products such as cheese. However, these high proteins in cow's milk can cause allergies in children. Reactions to proteins in cow's milk by immunological mechanisms are called cow's milk protein allergy (CMPA). There are studies on alternative possibilities against this negative situation by developing alternative milk types to cow's milk or various processes applied to cow's milk against CPA [9, 10], which has increased especially in young children in recent years. In this section, cow's milk allergy and alternative milks are discussed.

Table 1: Protein concentration of some mammalian milks (g/L) [3]

Protein	Human	Cow	Ewe	Goat	Donkey	Mare	Camel
Caseins							
α_{S1}-CN	0.3-0.8	10-15	3-6	0-7	0.2-2	2.5	5
α_{S2}-CN	Not detected	3-4	9-12	4.2	0.2	0.2	2.2
β-CN	1.8-4	9-11	19-28	11-18	3.9	11	15
κ-CN	0.6-1	3-4	4-5	4-4.6	Not detected	4.6	0.8
Whey proteins							
β-LG	Not detected	3-4	5.6-7.2	2.1	3.2-3.7	3	Not detected
α-LA	1.6	1-1.5	1.7	1.2	1.8-3	3.3	3.5

II. COW'S MILK ALLERGY

Cow's milk protein allergy, known as CMA or CMPA, which is one of the most common food allergies in childhood, affects approximately 3-8% of the total pediatric population in various countries around the world [11, 12]. Cow's milk protein [13], which causes anaphylaxis in young children, ranks third (8-15% cases) among all food allergens [13, 11]. Studies have shown that the number of fatal reactions from CMPA in children is quite high [14, 15, 16, 17].

CMPA can generally be classified as IgE-mediated reactions, non-IgE-mediated reactions, and the reaction formed by the combination of two reactions (Table 2) (Pereira, 2014).

IgE-mediated food allergy reaction is the best-known and most characterized type of food allergy [18, 19]. These reactions occur immediately after consumption of milk and there are two stages in its formation: the initial sensitization stage and the allergic reaction stage. The sensitization stage occurs in the allergic patient who is first exposed to milk allergens. Antigen-producing cells (APC) take proteins and convert them into smaller peptides and deliver them to naive T cell receptors (TCR) specific for a particular peptide on surface MHC II molecules [20]. Naive T cells are cells produced by the thymus that are mature but have not yet encountered its antigen. Naive T cells have unique TCRs specific to certain antigens [21, 22].

T cells activated by the ingestion of the allergen protein cause both the formation of IgE-producing cells and mastocytosis. Mastocytosis is a disorder that occurs with the proliferation and accumulation of mast cells in the intestines [23, 24]. Food allergen specific IgE binds to FcεRI receptors on the surface of tissue mast cells [20]. The second stage of allergic reaction takes place in the following days and results in inflammatory mediators released as a result of allergens interacting with IgE, causing symptoms such as hives, vomiting, swelling and difficulty breathing

Table 2: Classification of CMPA

Non-IgE mediated	IgE mediated	Mixed (IgE and non-IgE mediated)
Mild to moderate symptoms	**Mild to moderate symptoms** Eg urticaria, flushing, peripheral angiodema, pruritus	Atopic dermatits
Cow's milk enteropathy		
Food protein-induced practitis/ proctocolitis	**Anaphylaxis** Eg respiratory (wheezing, stridor) and/or cardiovascular (hypotension, tachycardia) compromise	Allergic eosinophilic oesophagitis
Food protein-induced enterocolitis syndrome (FPIES)		Eosinophilic gastritis
Heiner syndrome		

Unlike immediate IgE-mediated reactions, non-IgE reactions occur 1 hour to several days after cow's milk ingestion [25, 26, 27, 28, 29, 30].

CMPA affects children more than adults. Because oral tolerance, which refers to the active suppression of the systemic immune response to a previously orally ingested antigen, is also induced as individuals develop [31]. It has been reported that 80-90% of children with CMPA are tolerant after the age of 5 as a result of the maturation of their immune and digestive systems [32, 33, 34]. In addition, it has been reported that the diversity and increase in the density of the intestinal microbiota with increasing age may play an important role in inducing cow's milk tolerance. The fecal microbiota diversity of children with food allergies in their early life is lower compared to healthy children. Indeed, the gut microbiota of the individual becomes stable after the age of 5 [35, 36]. A microbiota that is adequately regulated in size and response early in life can generate a Th2 cell population that is fully responsive to oral tolerance induction, thereby preventing the development of allergy in 5-year-old children with CMPA [34, 35, 32, 37, 38].

There are more than 20 protein components in cow's milk that can aid in antibody production [39]. The allergic reaction that develops in children is usually dependent on more than one protein. Patients with CMPA are usually sensitive to one or more allergens. Studies have shown that only 27% of patients with CMPA are sensitive to only one, 15% to two allergens, 20% to three allergens, 22% to four allergens, and 16% to five allergens [3].

Cow's milk contains a lot of casein and serum protein that can trigger allergic reactions [40]. Studies have shown that the most common allergens detected in CMPA patients are caseins (especially αS1-casein), β-lactoglobulin and α-lactalbumin [41, 42, 43]. In addition, it is stated that other proteins such as bovine serum albumin and even lactoferrin can be potential allergens [44, 45]. Some properties of cow's milk allergens are given below:

1. **Casein Proteins:** Casein, which makes up 80% of milk proteins, is mainly composed of αs1-, β-, α_{s2}- and κ-casein fractions. The γ-casein fraction, which is very scarce in milk, is formed by the proteolysis of β-casein by the plasmin enzyme. Biological function of casein transport of calcium and phosphate. Casein is a conjugated protein with low solubility at pH 4.6 and consists mostly of phosphate groups esterified with serine amino

acids [15]. While αs- and β-casein fractions are sensitive to calcium, κ-casein is the casein fraction insensitive to calcium [15, 46]. Casein proteins found in colloidal form in cow's milk are composed of particles with a diameter of 20-600 nm. These particles are called casein micelles [7, 46]. Casein also contains high levels of the amino acid proline. Calcium, phosphorus, magnesium, sodium, potassium, and citrates are also found in the structure of casein micelles [47]. All casein fractions exhibit low solubility at pH 4.6, forming clots.

It is accepted that the main allergen in milk proteins is caseins, especially α_{S1}-casein [41]. In addition to the fact that caseins have a primary protein structure, the presence of micelles in milk also makes it heat-stable. This ensures that casein in bovine milk remains allergenic after heat treatment and becomes the most common allergen [48, 49]. Casein fraction is thought to cause permanent allergy [50, 51].

In a study to identify the major IgE and IgG binding sites of αS1-casein in CMPA patients, epitopes that bind 6 major and 3 minor IgE and one minor IgG on αS1-casein were identified [52]. Vila et al. [53] allergic children with persistent allergy symptoms stated that the level of IgE antibodies in the blood of children is higher than that of normal children. Jarvinen et al. [54] detected 5 IgE-binding epitopes in the blood of patients with persistent ISPA and they determined that two of them are α_{S1}-casein, one is on α_{S2}-casein, and one is on κ-casein.

2. **Whey Proteins:** Whey proteins, which make up approximately 20% of milk proteins, are composed of α-LA, β-LG, lactotransferrin and immunoglubulins.

   - **Lactoglobulin:** β--LG is the most important soluble protein in milk and constitutes approximately 50% of cow's milk serum proteins. With a molecular weight of k 18350 Da, β--LG consists of 162 amino acids. The structure of this globular protein, which shows a monomeric form in acidic and basic conditions, is stabilized by two disulfide bonds [55, 56]. In addition, there is a disulfide group involved in disulfide exchanges between -SH groups of other serum proteins and caseins [57, 58]. This protein, which is defined as one of the best lipid-binding proteins is capable of binding many molecules such as retinol, β-carotene, saturated and unsaturated fatty acids, and aliphatic hydrocarbons [59]. β-LG, which has a very high content of essential amino acids, is resistant to stomach digestion. Due to this feature, it does not hydrolyze in the stomach and produces high molecular weight peptides. These peptides arrive intact in the intestinal mucosa. It is anticipated that this may cause allergic reactions [46].

     Some studies claim that the strongest cow's milk allergen is β-lactoglobulin. Because this protein is not found in human milk, it has been determined that 60-80% of CMPA patients are sensitive to β-lactoglobulin [60]. Some other studies have shown that lactoglobulin is the main allergen in 66% of milk-sensitive patients, followed by caseins (57%) and α-lactalbumin and bovine serum albumin (18%) [61, 62]. Since birth, the IgE response is first to β-lactoglobulin, then to caseins and α-lactalbumin. However, it has been reported that the IgE response to caseins becomes dominant before the age of one, and the IgE response to lactalbumin occurs after one year of age [64].

Sel'o et al. [65] examined tryptic and synthetic peptides in the blood of 46 allergic patients to identify allergenic epitopes in the β-LG structure. As a result of the research, β-LG is a common pattern of multiple epitopes within the molecule path found. Another study using synthetic peptides spanning the amino acid sequence of β-LG identified 7 different IgE epitopes and 6 IgG binding sites [54]. These epitopes were found to be quite similar to the epitopes described by Selo et al. [65].

- **α-Lactalbumin:** α-LA is a monomeric, globular protein that forms 25% of serum proteins, belongs to the lysozyme family and has the ability to bind calcium. Its molecular weight is 14200 Da and consists of 123 amino acids. Due to the presence of 4 disulfide bridges in its structure heat stability of α-LA is higher than β-LG with 2 disulfide bonds [66, 67]. The high affinity for calcium binding of this protein is highly effective in the stability of the secondary structure. α-LA glands and has been found in all milk analysed to date [15].

  The amino acid content of this protein fraction is similar to that in breast milk [66, 67]. However, although the chemical structure is similar to breast milk, IgE-binding epitopes were observed in the patient in studies. In addition, these epitopes were not found in patients with persistent CMPA [46, 68, 69]. With all these aspects, the role of α-LA in cow's milk allergy has not been fully elucidated yet.

- **Bovine Serum Albumin:** Bovine serum albumin is a whey protein with a molecular weight of 66.4 kDa, constituting approximately 5% of serum proteins. Although this protein is very similar to human blood serum albumin physically and immunologically main functions are metabolism, transport, distribution of ligands and protection from free radicals. There are 17 disulfide bonds in bovine serum albumin. These disulfide bonds have an important place in the preservation of natural antigenic forms in the structure of bovine serum albumin [70, 71]. Disulfide bonds in the structure of bovine serum albumin have an important role in the preservation of natural antigenic determinants [70]. Epitopes identified in studies investigating the antigenic potential of fragments released by proteolysis of bovine serum albumin have been found to be inconsistent [72]. On the other hand, it has been reported that the 524-542nd peptides can form the most critical sequence in terms of allergy, however, epitopic areas can change when antibodies from different animal species are used [73]. Bovine serum albumin is effective in both beef allergy and CMPA [74].

- **Lactoferrin:** Lactoferrin is an iron-binding milk protein with a molecular weight of 76 kDa and the amount in milk is mostly below 1%. The main task of lactoferrin is by binding iron; removes iron from the environment and protect the organism from infection [75]. In the studies conducted, many hypotheses have been established in order to have information about whether lactoferrin has an effect on allergy, and as a result, IgE epitopes have been determined. However, another possibility is that the patients in the studies may have formed IgE against all CMP [46, 50].

- **Immunoglobulins:** The immunoglobulin fraction of milk constitutes 1% of total milk proteins and 6% of serum proteins. The basic structure of immunoglobulin has a Y-shaped structure consisting of 4 polypeptide chains linked by intramolecular or intermolecular disulfide bonds. Cow's milk immunoglobulins are composed of 3 isotopes called IgG, IgA, and IgM [76]. Three different types of immunoglobulins belonging to the IgG class, IgG1, IgG2, and IgG3, have been defined in cattle [77, 78]. Findings about the immunoglobulins in cow's milk being allergens are very limited. Still, studies have shown that IgE binds to IgG. Based on this, it is thought by researchers that it may cause allergy [79, 80]. However, regarding the epitopes of IgG to which T and B cells will bind, since it has not been clarified yet, IgG has not yet been considered a milk allergen [70].

The difference in the structural composition of breast milk and cow's milk can be seen as the main cause of the allergic effect. This difference is also due to the fact that the protein content of breast milk is quite low compared to cow's milk. In addition, while breast milk is rich in serum proteins, the proportion of casein in cow's milk is higher than in breast milk. While this allows breast milk to be digested easily, the hard clot that will form in the stomach due to the high amount of casein makes it difficult to digest cow's milk and causes allergies [81, 82]. In addition, cow's milk is resistant to pepsin hydrolysis because it contains β-LG, which is not found in breast milk. For this reason, β-LG, which first enters the intestinal mucosa and then enters the blood, causes allergic reactions [66, 83]. On the other hand, immunological substances found in breast milk at a higher rate than in cow's milk prevent the formation of milk allergy [26,42, 81, 82]. For all these reasons, CMPA is more common in infants who cannot breastfeed.

III. ALTERNATIVE MILKS FOR CMPA

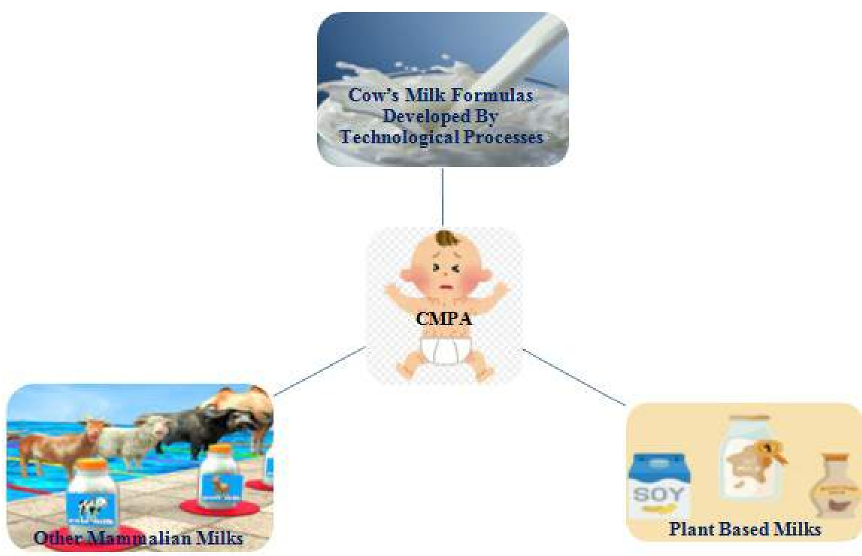

Figure 1: Cow's Milk Alternatives

In the treatment of CMPA, it is recommended to exclude milk and dairy products from the diet first. However, milk and dairy products have a very important place in adequate and balanced nutrition, especially in children. Removing these products from the diet can lead to nutritional problems [84, 85, 86]. Therefore, research on the development of possible alternatives to cow's milk have been conducted in recent years [26, 87, 88, 89, 90]. Alternative milks to cow's milk can be examined in three groups: Cow's milk formulas developed by technological processes, mammalian milk alternatives and plant-based milks [91] (Fig1).

1. **Cow's Milk Formulas Developed by Technological Processes:** Many processing technologies are used to reduce allergenicity in dairy products. These processes consist of processing technologies such as hydrolysed cow’s milk formulas, lactic acid fermentation, high-pressure application, maillard reaction and heat treatment [42].

   - **Hydrolysed Cow’s Milk Formulas:** Hydrolysed cow's milk formulas are divided into two groups: The first group includes formulas based on heavily hydrolysed cow's milk protein (EHF) derived from bovine caseins or whey proteins. These products can be tolerated by approximately 95% of patients with ISPA. The products in the second group consisted of synthesized free amino acids (AAF). Milk in this group can be tolerated by the majority of patients with ISPA [92].

   - **Extensively Hydrolysed cow's milk Protein-Based Formulas:** In the preparation of EHF, proteolytic enzymes of animal origin such as pepsin, trypsin and chymotrypsin, vegetable origins such as papain and bromelain, or microbial origins such as alkalase and substilisin are used [93]. Thus, proteins are pre-digested outside the body. For this reason, EHF, which is both well-tolerated and nutritionally adequate, has become the preferred formula for feeding infants with CMPA [88, 94, 95]. However, its high costs and bitter taste limit its consumption [96, 97, 98, 99]. The bitter taste of EHF is related to the fact that it contains peptides of less than 1000 Da consisting of hydrophobic amino acids [100, 101, 102].

     It has been reported that the short peptide chains in the structure of EHF can potentially cause allergic reactions in 5-10% of patients, therefore EHF should not be used in children who are hypersensitive to cow's milk proteins or have a history of anaphylaxis [86, 103, 104].

     It has been reported that the most effective enzyme to reduce the allergenicity of β-LG is trypsin or the combination of trypsin and pepsin and chymotrypsin. The combined application of heat treatment and enzymatic hydrolysis is also effective in reducing the allergenicity of β-LG [70, 105]. By using pepsin and chymotrypsin, the allergenicity of both α-LA and β-LG can be reduced. The degree of hydrolysis of these proteins varies between 1% and 20%, depending on the enzyme type and hydrolysis time [61, 70]. Points to be considered in the production of EHF; avoidance of excessive hydrolysis to prevent bitter taste [106] and milk proteins other than β-lactoglobulin are not susceptible to trypsin digestion [70, 107, 108].

     It has been determined that the use of microbial-origin enzyme preparations containing endo and exo-peptidases in the production of EHF improves both organoleptic and antigenic properties of EHF [93, 109]. Another method is the continuous hydrolysis of cow's milk proteins with immobilized enzymes prepared using reactor systems [61, 109]. Another innovative technique is the hydrolysis of milk proteins with probiotics. Studies have shown that probiotics, such as *Lactococcus lactis Lactobacillus rhamnosus* and *Bifidobacterium lactis*, reduce allergenicity [61, 110, 111].

Bonomi et al. [105], β-LG (Bos d5), Monaci et al. [70] found that allergenicity of β-LG and α-lactalbumin reduced by hydrolysis using trypsin alone or in combination with chymotrypsin and pepsin. Liang et al. [112, 113] stated that the allergenicity of casein, β-lactoglobulin and α-lactalbumin decreased after enzymatic hydrolysis using alkalase and protamex. Oliveria et al. [114] reported that casein allergenicity was reduced by using latex peptidases. Kaur et al. [115] determined that the allergenicity of β-lactoglobulin decreased by using actinidin protease obtained from kiwifruit.

- **Amino Acid-Based Formulas:** AAFs are considered to be the only non-allergic milk formulas with free amino acids in their structure and are used safely in hypersensitive patients who cannot tolerate other formulas [86]. The free amino acids contained in AAF do not only consist of peptides obtained from cow's milk proteins. Therefore, it can be considered the second option after EHF for children with severe CMPA [116]. AAF formulas are also used as an alternative for patients with multiple food allergies [88, 99].

  It has been reported that children with severe ISPA can tolerate the hypoallergenicity of AAF [117, 118]. Studies have shown that when compared to other formulas, the development of babies fed with AAF is similar to the development of healthy babies and it supports the normal growth of children [119]. The disadvantages of these products are their low taste and high cost [86, 92, 99].

- **Heat Treatment:** Heat treatment is a process applied to increase the safety of the product in terms of health by destroying pathogens and extending the shelf life of the product by reducing the microorganisms that cause spoilage [120]. During heat treatment, important structural and chemical changes occur such as protein denaturation, aggregation and Maillard reactions. These changes may also have some effect on the allergenicity of proteins.

  Casein has the highest thermal stability among milk proteins. This is followed by α-LA, β LG, bovine serum protein and immunoglobulins follow. While heat treatment at 120ºC for 15 minutes does not affect the antibody production of casein, heat treatment at 70-80ºC or 100ºC completely abolishes the allergenicity of bovine serum albumin and Ig [120].

  Baldo [63] determined that 15 minutes of heat treatment at 80 and 100ºC caused a decrease in the fixation ability of IgE, bovine serum albumin and β-LG, but no change in α-LA and casein. In another study, it was determined that the IgE binding performance of β LG decreased slightly in milk heated to 74ºC, whereas there was a more significant decrease at 90ºC [121]. On the other hand, the denaturation of β LG also resulted in the formation of some new epitopes [122].

Bu et al. [123] determined that antibody formation increased as a result of the exposure of allergenic epitopes in natural molecules due to denaturation of α-LA and β-LG as the temperature increased from 50 °C to 90 °C. However, the ability of both proteins to form antibodies decreased significantly above 90ºC. The reason for this decrease is thought to be the masking or aggregation of epitopes exposed on the surface of the molecule as a result of aggregation and sulfhydryl/disulfide changes that occur during heat treatment [57]. On the other hand, it was determined that the antigenic property of α-LA decreased by 25% when heat treatment was applied at 120ºC for 20 minutes. This is because the ability to form antibodies is reduced due to the loss of epitopes as a result of the Maillard reaction occurring at high temperatures [122]. On the other hand, this reduction may also be associated with decreased protein solubility [124]. Similarly, Kleber and Hinrich [57] also determined that the antibody-forming property of β-LG in skimmed milk and sweet whey increased when the temperature was increased from 50ºC to 80ºC and decreased when it exceeded 90ºC.

Research results show that high-temperature applications reduce antibody formation of cow's milk proteins. However, high-temperature applications do not affect the antibody-forming ability of casein [125], although denatured β-LG has been reported to promote immunological reaction in the intestinal mucosa compared to native β-LG [126]. In addition, even if very high heat treatment applications reduce the allergenicity of milk proteins, it can cause losses and undesired changes in both the nutritional value and sensory properties of the product. Therefore, further studies are needed to investigate the effects of heat treatment on allergens.

- **Maillard Reaction:** The Maillard reaction is a non-enzymatic browning reaction that occurs between reducing sugars and amino acids during food processing. With this reaction, the functional properties of proteins can be improved as well as their allergenicity can be eliminated. Studies have shown that the epitope domain of β-LG binding to lactose as a result of the Maillard reaction changes [127] and its IgE binding ability is reduced. It has been reported that this decrease is related to the degree of binding and the amount of modified amino acid groups [128]. However, it has been reported that conjugation of β-LG with acidic oligosaccharides increases heat stability and as a result of this conjugation, the coating of epitopes reduces the ability to form antibodies [129].

Molecular weight and amount of sugars attached to proteins are very important in reducing the antibody formation ability of proteins by the Maillard reaction. Wróblewska and Jedrychowski [130] determined that the increased amount of polyethylene glycol as a result of the conjugation of serum proteins with polyethylene glycol decreased the immunoreactive properties of serum proteins. Hattori et al. [131] concluded that conjugation of β-LG with carboxy methyl dextran the allergenicity of β-LG decreased with the increase of carboxy methyl dextran content. A similar result was obtained by Kobayashi et al. [132]. Based on these results, it can be said that conjugation with sugars with high amounts and molecular weight can be quite effective in reducing the antibody formation feature of proteins.

The degree and reaction conditions of the Maillard reaction have an effect on the allergenic properties of milk proteins. β-LG and α-LA antigenicity could be reduced by over 90% with the Maillard reaction performed by conjugation of serum protein isolates with glucose under optimum conditions [62]. Although studies have shown that the Maillard reaction performed under controlled conditions will reduce the allergenicity of milk proteins, this reaction needs to be applied carefully because of its potential disadvantages such as colour and taste changes and losses in amino acid lysine, as well as its ability to form new epitopes due to conjugation.

- **High-Pressure Application**: With the application of high pressure, which is one of the food preservation methods, it is possible to reduce the microbial population as well as to preserve temperature-sensitive components such as vitamins, sensory and nutritional properties [62]. The application of high pressure, which causes structural changes in milk proteins such as denaturation and formation of β-LG aggregates, can reduce the allergenic potential of milk [134]. During the application of high pressure, hydrophobic bonds and salt bridges are destroyed, and then the proteins are denatured. Changes that occur in proteins as a result of high pressure depending on the natural structure of the protein as well as pH, temperature, ionic forces, and the severity of the applied pressure [134, 135]. The application of high hydrostatic pressure can accelerate the enzymatic hydrolysis of proteins and reduce the ability of hydrolysates to form antibodies [136].

  Studies have shown that applying pressure between 0.1 and 300 MPa increases the hydrolysis of β-LG by the enzymes chymotrypsin, pepsin, and thermolysin [62, 137, 138, 139] However, increasing the pressure above 500 MPa caused the complete unfolding of the secondary protein structure of β-LG [140] and the formation of soluble disulfide-bound aggregates [141].

  When heat treatment (60 min at 50 ºC) and high pressure (600 MPa) are applied together, it has been determined that the β-pleated structure of β-LG turns into an α-helix structure [142]. On the other hand, by combining enzymatic hydrolysis with high-pressure application, the allergenic properties of serum protein hydrolysates can be significantly reduced [105, 103, 143]. Penas et al. [62] stated that the high pressure (300 MPa) applied before or during enzymatic hydrolysis with corollase PN-L and neutralase enzymes reduces the allergic properties of cow serum protein hydrolysates. In another study, it was shown that different high-pressure (200-300 MPa) and different heat treatment (30-68°C) applications increased the antibody formation ability of β-LG.

  Studies have shown that the application of high pressure during the hydrolysis of milk proteins can be used as an effective method to reduce the allergenicity of serum protein hydrolysates.

- **Lactic Acid Fermentation**: Lactic acid bacteria with a proteolytic system can break down milk proteins during fermentation and reduce the allergenicity of milk proteins. With fermentation, the digestion of hydrolysed milk proteins is facilitated, and bioactive compounds are formed. In addition, as a result of the fragmentation of some epitopes, allergenicity is reduced [144, 145].

In some studies, it has been found that using only probiotic bacteria in the fermentation process can reduce the allergenicity of proteins [70]. Researchers have determined that *Lactobacillus* GG alleviates intestinal inflammation in patients with atopic dermatitis and food allergies [146]. Bu et al. [133] determined that the antigenicity of α-LA and β-LG in skim milk fermented with *Streptococcus thermophilus* and *Lactobacillus helveticus* strains was significantly reduced. Tzvetkova et al. [147] also determined that 21 strains of lactobacillus isolated from yoghurt promote the degradation of milk allergens. In another study, it was found that after fermentation of sterilized cow's milk, the antibody-forming properties of serum proteins decreased, but there was no change in their allergenicity [148].

2. **Mammalian Milk Alternatives:** There are many studies on which milk can be closer to breast milk, except for cow's milk, which is obtained from other mammals [149]. The sequence identity (%) of milk proteins of different mammalian species is given in Table 3

- **Ewe's Milk:** Ewe's milk contains approximately 50% more dry matter than cow's and goat's milk, and its fat content (~6.4%, w/w) is much higher than these milks. The lactose and mineral content in its composition is also higher than cow's, goat's, and human milks [86] [150]. The average protein content of ewe's milk (5.6%) is also higher than that of cow's and goat's milk. The protein fraction found at the highest rate in ewe's milk is β-casein as in goat milk (Table 1). The amount of other protein fractions in ewe's milk is also higher than in cow's milk, with the exception of α_{S1}-casein (Table 3). The β-LG ratio in ewe milk is close to twice that of cow milk [151, 152, 153].

Ewe's milk is a valuable milk used in the production of special cheeses due to its high protein, fat content and unique taste. Although ewe's milk is seen as an alternative milk for CMPA patients, it is not a suitable substitute because its protein structure (both casein and serum proteins, especially b-casein) is very similar to cow's milk [3]. It was determined in immuno-electrophoretic analysis that antibodies to cow's milk proteins could recognize the main part of ewe's and goat's milk proteins, whereas mares' and donkey's milk proteins showed poor cross-reactivity [154]. Likewise, in some in vivo studies, 98% of 26 children with CMPA were also allergic to ewe's milk casein [155, 156].

Spuergin et al. [157] also determined a cross-reaction between the α-caseins of cow's and ewe's milk. The researchers noted that ewe and goat milk α-casein was recognized by IgE antibodies in the serum of allergenic children. Vojdani et al. [158] stated that camel milk and vegetable milk would be suitable as alternative milk for individuals with CMPA, while ewe and goat milks had similar allergic effects as cow's milk. Nachshon et al. [159] reported that individuals who tolerate cow's milk can also tolerate goat and ewe milk. However, most studies have shown that ewe's milk is unsuitable for infants due to its composition and similarity to cow's milk proteins [19, 154, 155, 160].

Table 3: Comparison of the sequence identity (%) of milk proteins of different mammalian species [3].

Protein	Human	Cow	Ewe	Goat	Donkey	Mare	Camel
Caseins							
αs1-casein	26.6%	100%	87.4%	86.9%	39.0%	38.2%	40.5%
αs2-casein	Not detected	100%	88.0%	87.5%	56.1%	53.1%	50.0%
β-casein	49.3%	100%	91.4%	90.9%	53.1%	53.1%	63.8%
κ-casein	49.4%	100%	82.5%	82.4%	51.8%	51.4%	53.5%
Whey proteins							
β-Lactoglobulin	Not detected	100%	95.7%	96.3%	56.2%	57.4%	Not detected
α-Lactalbumin	75.6%	100%	96.7%	94.3%	71.5%	72.4%	69.1%

It has been reported that ewe's milk and cheeses may rarely induce a specific allergy not related to cow's milk proteins [26]. Pazheri, et al. [161] determined that an anaphylactic reaction occurred with the consumption of Romano and Ricotta cheeses in two children with ewe milk allergy. In their experiment, the researchers determined that a child with CMPA and the other without CMPA determined that child without CMPA could consume cow's milk without cross-allergenicity, but allergic reactions occurred when the child with both CMPA and ewe milk allergy consumed milk. In another case, anaphylactic reactions were reported in identical twins who did not have CMPA but were allergic to ewe’s and goat’s milk [162].

- **Goats Milk:** Although the composition of goat's milk is similar to cow's milk, its protein and fat fractions are easier to digest than cow's milk [86, 163, 164]. While the amounts of saturated fats and trans fatty acids in goat's milk are similar to cow's milk, the amount of short and medium-chain fatty acids in its composition is higher than in cow's milk. Because goat milk and its products do not contain α_{S1}-casein, it has long been considered a potential alternative to patients with CMPA [91, 165, 166]. However, since the amounts of k-casein and β-LG are similar to cow's milk, it is not currently recommended as a suitable substitute (Table 3).

The researchers determined that it is difficult for children with CMPA to tolerate goat's milk due to the cross-reactivity between bovine and goat milk proteins in vitro and in vivo analyses. In vitro experiments for children younger than 80 months (n = 21) have shown that the caseins in goat milk are identified by specific IgE binding [167]. In vivo studies have shown that children aged 5 months to 7 years with IgE-mediated CMPA have positive responses to cow's and goat's milk in skin testing. Bellioni-Businco et al. [168] in their study with 58 allergic children reported that the dose of goat's milk required to initiate the reaction in CMPA patients was significantly higher than that of cow's milk. Vita et al. [169] stated that there was no improvement in the clinical symptoms of allergic children who consumed goat milk, unlike children who consumed donkey milk. These data show that goat's milk is not suitable to replace cow's milk for allergic children. For this reason, it is recommended to include a warning on the label of products containing goat's milk that these products are not safe for children with CMPA in order not to cause serious allergic reactions in infants with CMPA.

Compared to CMPA, goat milk allergy is rarely seen. Goat milk allergy has been defined as a rare disease in which aS1-, aS2- and b-caseins are considered the main allergens [170]. This type of allergy is mostly seen in patients older than 1 year and occurs in patients with CMPA or multiple food allergies [171]. Goat milk creates a softer and more digestible clot in the stomach than cow's milk due to the low as1-casein content in its composition [172]. This causes a shorter retention time in the digestive system and limits the amount of allergen reaching the mucosa. Likewise, the serum proteins in goat milk are digested in a shorter time [172]. Zhang et al. [173] also reported that cow's milk is more allergenic than goat's milk because of the structural differences in αS1-casein in cow and goat milk.

- **Donkey's Milk:** It is estimated that the share of a donkey (Equus asinus) milk among the milk produced in the world is less than 0.1%. It is reported that donkey milk is used in some regions for the treatment of various diseases such as asthma, bronchitis, gastritis, joint pain, and healing wounds [174, 175].

  It can be distinguished from breast milk by certain physicochemical properties. The fat content of donkey milk is quite low compared to other types of milk and therefore the energy it gives is less (~39.68 kcal). However, the polyunsaturated fatty acids in its structure ensure that the nutritional quality of donkey milk is higher than that of cow's milk. In addition, the fact that the ratio of saturated acids in donkey milk is lower than that of cow milk increases its nutritional value [86, 150, 151]. Donkey milk's high content of lactose (~6.3% w/w) provides better flavour and facilitates calcium absorption [151, 176]. The mineral content of donkey milk is quite low compared to cow's milk (~0.4% w/w). The protein ratio of donkey milk is ~1.91%. Since the ratio of albumin and globulin is more than 1/3 of the total protein, the protein ratio of casein/whey (47.28%/36.96%) in donkey milk, which is in the group of albuminous milks, is lower than all milks except breast milk [151]. The main protein fractions of donkey milk are β-casein (3.9g L^{-1}) and β-LG (3.7g L^{-1}). The amount of a-lactalbumin in donkey milk is also around 3.0 g L^{-1} (Table 1). Donkey milk contains α_{S1}-casein and α_{S2}-casein in varying amounts from 0.2 to 2.0 g L^{-1}. The most important difference of donkey milk from other mammalian milks is the absence of k-casein (Table 3) [164]. Because of these properties and high palatability, donkey milk can be considered as an alternative milk for children with CMPA, despite the high β-LG and α-LA ratio in its composition [175, 177, 178, 179].

  Donkey milk, which is highly tolerated by children with CMPA, can be used for a long time in both IgE-mediated and non-IgE-mediated children with CMPA. However, donkey milk proteins may have a risk of cross-reacting with cow's milk proteins it should be used under the control of a nutritionist [181, 182]. Immunochemical analyses have shown that donkey milk caseins are poorly recognized by IgE from children with CMPA and this milk can be tolerated by infants [181]. Monti et al. [182] investigated the sensory acceptability and allergenicity of donkey milk by giving 200-500 mL of donkey milk per day to 46 children with CMPA. They reported that 82.6% of the children liked and tolerated this milk after a while, and 17.4% showed hypersensitivity. Carrocio et al. [183] added donkey milk to their diets in the treatment of 21 children aged 2-3 months who showed symptoms associated with CMPA and were intolerant to hydrolysed cow's milk proteins.

Researchers reported that 86% of the patients showed clinical tolerance and allergy tests were negative. In other studies, it was shown that children with CMPA could tolerate donkey milk well, and it provided an improvement in children's weight and height [184, 185].

It is reported that donkey milk has positive effects on health as well as being tolerated by patients with CMPA. For example, it was determined that the clinical symptoms of children with atopic dermatitis and CMPA who consumed donkey milk improved [169]. Donkey milk contains plenty of lysozyme (13.13-15.34% of total protein) compared to other types of milk [186]. In a study [187], it was claimed that both colostrum and normal milk of donkeys show immunological activity, and it is noted that they can be useful in the treatment of diseases related to the immune system in humans and the prevention of atherosclerosis [188]. A recent study found similar concentrations of pyroglutamic acid in human and donkey milk. Pyroglutamic acid is claimed to be effective against diabetes because it is associated with the regulation of glycolysis [189]. It has been reported that donkey milk, which has beneficial biofunctional properties in the regulation of the immune system, has beneficial effects in terms of throat health, especially in children, the elderly, and patients in the recovery period [190]. In-vitro studies have shown that donkey milk can stimulate nitric oxide production and release of, IL-1β, IL-10 IL-12 and TNF-α, IgA and IgG from human monocytes, thus maintaining immune homeostasis [191]. Studies have reported that donkey milk also shows anti-tumour and anti-proliferative activity [187], and also has a very strong angiotensin-converting enzyme (ACE) activity [192].

Studies have proven that donkey milk is a suitable alternative in the nutrition of children with CMPA due to its hypoallergenic feature. It has been reported that the tolerance of donkey milk by children with CMPA and its low allergenicity are associated with protein fractions [193]. It has been reported that the allergenicity of donkey milk is lower because the amino acid composition of the IgE-binding linear epitopes in cow's milk proteins is different in the regions to which they correspond in donkey milk [181, 196, 194]. However, donkey milk is not suitable for use in hypoallergenic formulas prepared for infants with CMPA due to its high content of β-lactoglobulin. Because a-lactalbumin in donkey milk is very similar to that in cow's milk, allergy may occur due to cross-reactivity between donkey milk and cow's milk proteins. In addition, feeding infants with CMPA with donkey milk may lead to nutritional problems due to iron deficiency or low-calorie intake [195]. More research is needed before donkey milk can be used safely as a substitute milk for children.

- **Mare's Milk:** The production amount of mare's milk, which is widely consumed in Central Asia and Mongolia, is 0.1% of the milk produced in the world [172]. Mare's milk contains 6.37% lactose, 1.21% fat, 2.14% protein and 0.42% mineral matter. Unlike donkey milk, mare's milk contains conjugated linoleic acid, one of the trans fatty acids (C18:2, cis-9, trans11). In addition, the amount of vitamin C in mare's milk (1287 to 8100 mg 100 g-1) is higher than in donkey milk [86, 150,151].

The casein content of mare's milk, which is in the group of albuminous milks, is low (Table 1). Although the composition of mare's milk is similar to donkey milk, the ratios of β-casein and κ-casein are much higher than that of donkey milk. The amounts of α-LA and β-LG in the mare and donkey milk are also similar. In some studies, it was stated that mare's milk can be used as an alternative to cow's milk for children with CMPA [196, 197, 198]. Mare's milk proteins have a lower sequence identity with cow's milk proteins than donkey milk (Table 3).

Because mare's milk is easily digestible, has low casein content, and has low similarity to cow's milk proteins in its composition, it has been proposed as a new alternative for infants with CMPA [199]. According to in vivo and in vitro tests by Businco et al. [196], mare's milk would be a good alternative for children with severe IgE-mediated allergies. Only two of the 25 children participating in the study had a positive skin test for mare's milk, and the others did not have an allergic response. In another study, it was determined that 96% of 25 children with IgE-mediated CMPA tolerated mare's milk, with only one patient testing positive [197].

On the other hand, it has been found that α-lactalbumin and β-lacto globulin, which are mare's milk proteins, can trigger an unusual and rare allergy that is not related to cow's milk protein allergy [200]. For example, skin contact allergy has occurred after the use of a cream containing mare's milk proteins [198].

- **Camel's Milk:** Camel milk is an important source for people living in arid and hot regions [201, 202, 203] has become very popular in recent years due to its high nutritional value and extraordinary therapeutic effects [203, 204]. Camel milk production accounts for 0.34% of total milk production in the world [205]. The bioactives of camel milk are beneficial for immune problems such as Crohn's infections and sclerosis, as well as health benefits such as hypocholesterolemia, anti-carcinogenic, anti-diabetic, anti-autism, hypoallergenicity [27, 206, 207, 208]. Numerous studies have shown that anti-inflammatory, anti-apoptotic, and antioxidant substances in camel milk improve alcoholic liver damage [209, 210, 211].

Although the amount of lipids and lactose in camel milk is similar to cow's milk [150], camel milk is distinguished from cow's milk by its high amount of vitamin C and vitamin B3. The amount of mineral substances in camel milk is also higher than in cow milk. The amount of protein in camel milk is between 2.5% and 4.9% [205]. The most important feature of camel milk is that it does not contain β-LG as in breast milk. Among other mammalian milks, camel milk is the only milk without βLG in its composition [203, 212, 213]. The ratio of α-LA in camel milk is around 3.5 g L^{-1} [214]. β-casein (15.0 g $^{L-1}$) constitutes the main protein fraction of camel milk (Table 1) [203]. Camel milk is easier to digest and has lower allergenicity than cow's milk because the protein fractions do not contain α_{S2}-casein and κ-casein [27]. The sequence identity of camel milk proteins with cow milk proteins is low (Table 3). Therefore, it is considered alternative milk for children with CMPA [27, 86, 207, 214].

Some studies on the allergenicity of camel milk proteins revealed that no cross-reactivity was observed between cow and camel proteins and that anti-β-lactoglobulin antibodies did not react with camel milk proteins. In addition, it has been determined that IgEs taken from children with CMPA recognize other milk proteins but not camel milk [153, 159]. El-Agamy et al. [214] also reported that no immunological cross-reactivity was observed between cow and camel milk proteins.

In vivo studies on animals have shown that camel and cow milk have low cross-reactivity [215]. Navarrete-Rodriguez et al. [216] determined that camel milk is tolerable and safe for children aged one year and older with ISPA and reported that it can be evaluated in milk formulas without causing any negative effects on their sensory properties.

As with other milks, an allergic reaction to camel milk may occur very rarely in hypersensitive individuals. For example, it has been reported that a child without CMPA in the United Arab Emirates had an anaphylactic reaction to camel milk proteins [217]. Findings from studies suggest that camel milk may be a tolerable and suitable alternative for children with CMPA. However, it is thought that more in vitro and in vivo studies are needed to make a definitive judgment.

3. **Plant-Based Milks:** Plant-based milk has become an important alternative to cow's milk due to medical reasons such as CMPA, lactose intolerance, coronary heart diseases, or because of the nutritional importance of the high amount of minerals, vitamins, and dietary fibre they contain, or due to the demands of vegetarian groups [86]. Plant-based milks can be classified into five main groups according to their raw materials: cereals (oats, rice), legumes (chickpeas, soybeans), nuts (almonds, Brazil nuts, cashews, hazelnuts), seeds (sesame, sunflower) and pseudocereals (quinoa) [218].

The chemical composition of plant-based milks is given in Table 4. These milks, whose nutritional value, sensory properties, and stability are different from cow's milk [218], are produced by breaking down the raw material, extracting it in water and homogenizing it [218, 219]. The properties of the raw material, the extraction method applied, and the storage conditions of the product affect the stability and particle size of the final product [219]. The general production steps of plant-based milks are given in Figure 2.

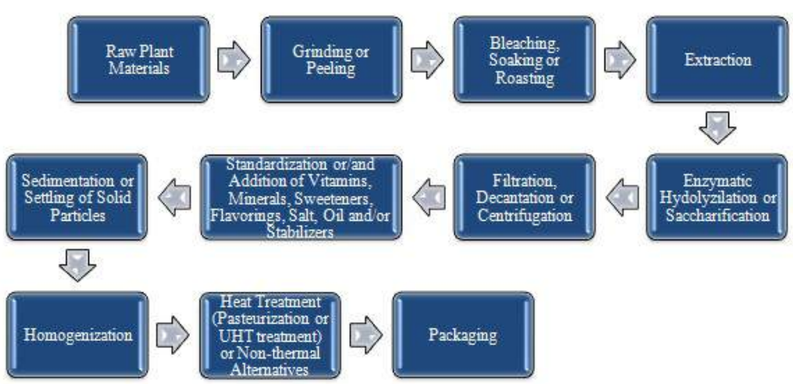

Figure 2: Production steps of plant-based milks

The first step in the production of plant-based milk is the wet grinding of the raw material followed by filtration to remove coarse particles. Some processes such as peeling, bleaching, soaking, or roasting of raw materials are needed to improve the quality and sensory properties of the final product [220]. Extraction is the most important step influencing the composition of the final product. At this stage, the extraction efficiency is increased by adding NaOH or bicarbonate as well as some enzymes. The enzymes used not only provide partial hydrolysis of polysaccharides and proteins but also make the extract sweeter without the need for added sugar [220, 221]. In the next step, the sediment in the beverage is separated by decantation, filtration, or centrifugation [221, 222]. Then, some ingredients such as flavourings sweeteners, salt, minerals, vitamins, oil and/or stabilizers are added to stabilize the final product and improve its quality [220]. One of the most important problems in herbal milk is the stability of the final product. The stability of the product depends on the size of the dispersed phase particles such as proteins, starch granules, oil globules and solid particles. [218]. Therefore, settling or sedimentation of solid particles is required. To achieve this, either the particle size must be reduced, or a stabilizer must be added [220]. Homogenization is applied to reduce the particle size and stabilize it. Heat treatments such as pasteurization and UHT are applied to make the final product durable and microbiologically safe. However, heat treatment may affect the taste, aroma, stability, and colour of the final product by causing changes in the properties of heat-sensitive vitamins and proteins [223, 224, 225]. For this reason, alternative non-thermal methods such as high pressure, microwave, UV sterilization, ultrasound and pulsed electric field applications are used to extend the shelf life of some beverages. The last stage is the packaging of the drinks with suitable materials.

Plant-based milks have advantages such as being free of cow's milk protein, cholesterol, and lactose, containing fibre and isoflavones, high in unsaturated fatty acids, and low in saturated fatty acids. However, it has disadvantages such as low protein and micronutrient elements, some proteins in its structure causing allergies, containing anti-nutrient elements and low consumer acceptance. Among plant-based milks, soy and nuts milks contain proteins that can cause allergies [226]. Studies have shown that approximately 14% of people with CMPA are also allergic to soy protein [227, 228]. On the other hand, long-term consumption of these milks instead of cow's milk can cause protein deficiency and serious diseases [220]. To overcome these problems, it may be recommended to fortify plant-based milks with protein or to mix more than one plant-based milk. Another method is the partial hydrolysis of proteins by enzymes. In addition, since applications such as soaking, bleaching and heat treatments applied during the processing of plant-based milks will cause the loss of some vitamins and minerals, these milks should be supplemented with daily foods [220, 229]. Antinutrients in plant-based beverages inhibit the absorption of nutrients and bind minerals, reducing their bioavailability and digestibility of protein [220]. Heat treatment, chelation, fermentation, germination or exogenous phytase treatments can be used to reduce antinutrients in plant milks [220, 230]. However, isoflavones found in legumes, especially soy, have positive effects on preventing osteoporosis, prostate cancer, and cardiovascular diseases [231, 232]. However, there are question marks about the effect of long-term consumption of soy-based beverages in early childhood [231, 233]. One of the major challenges with plant-based milks is low consumer acceptability. These milks are described as "beany" and "painty" because of the mouthfeel they leave [234]. Processes such as blanching, roasting, and alkaline immersion reduce the bean flavour in legume-based milks [222].

Table 4: Chemical composition of Plant-based milks and cow's milks [235]

		Carbohydrates (g)	Protein (g)	Total Sugar (g)	Total Lipids (g)	Total Fibers (g)	Calcium (g)	Energy (Kcal)
Cow' milk		5.42	3.33	5	3.33	0	129	67
Soybean	Raw materials	36.67	36.67	0	33.33	16.7	133	500
	Aqueous Extract	3.75	3.33	2.5	1.88	0.8	188	46
Chickpea	Raw materials	27.5	8.75	0	2.5	13.8	50	175
	Aqueous Extract	2.32	1.21	-	0.34	0.78	-	-
Almond	Raw materials	21.43	17.86	7.14	50	10.7	214	571
	Aqueous Extract	7.92	0.42	7.5	1.04	0.4	188	42
Hazelnut	Raw materials	40	13.33	3.33	40	6.7	200	567
	Aqueous Extract	3.1	0.4	3.1	1.60	0.3	120	121
Rice	Raw materials	77.78	6.67	0	0	0	0	356
	Aqueous Extract	9.5	0.1	3.3	1.00	0	120	47
Oat	Raw materials	67.5	12.5	2.5	6.25	10	0	375
	Aqueous Extract	2.09	7.5	0.9	1.67	0.63	7.5	41.7
Sesame seed	Raw materials	46.67	10	0	36.67	3.3	200	567
	Aqueous Extract	4.04	2.97	-	6.43	-	-	-
Sunflower seed	Raw materials	23.33	20	6.67	50	10	133	633
	Aqueous Extract	0	0.78	-	2	1.2	0.16	21.08
Quinoa	Raw materials	20	2.86	2.14	1.79	2.1	14	107
	Aqueous Extract	3.5	0.5	0.3	1.2	-	-	121

Legume Based Milks

- **Chickpea Based Formula:** *Chickpeas* contain high levels of protein, carbohydrates, vitamins, minerals, and fibre (Table 4) [236]. In addition to being easier to digest than other legumes, the high iron content, and the low amount of antinutrients have made chickpeas popular recently [237, 238]. The soluble and insoluble fibres in the composition of chickpeas have a prebiotic effect as well as lowering total cholesterol and low-density lipoprotein (LDL) [237, 239]. The lipids in chickpeas contain high levels of unsaturated fatty acids. [240]. Chickpea, which is rich in vitamins and minerals, also has anti-nutrients that can be eliminated by different cooking techniques [244, 239]. Although chickpea proteins are limited in terms of sulphurous essential amino acids, the biological value of proteins is higher when compared to other legumes [241]. The parameters affecting the quality during the processing of chickpeas are temperature, processing time and humidity level [240]. It has been reported that heat treatment above 120 °C for more than 10 minutes reduces the emulsification ability and stability of chickpea proteins while increasing the foam stability [241].

Chickpea milk can be considered alternative milk to cow's milk because it is both delicious and economical in child nutrition and treatment [236].

- **Soy Based Formula:** Soybean, which is a rich source of proteins, carbohydrates, and lipids, contains high levels of polyunsaturated fatty acids, minerals, and vitamins, while it does not contain cholesterol (Table 4) [242, 243]. Soy protein contains all of the essential amino acids [244]. Thanks to their high levels of phytochemicals, soy products reduce the risk of certain cancers, osteoporosis, and other non-communicable chronic degenerative diseases, as well as cholesterol levels [218, 245]. The most important problem in consuming soy formulas is that allergy is common because it contains proteins that can cause allergies and approximately 14% of patients with CMPA also react to soy proteins [227, 228]. Although soy-based formulas are tolerated by children with CMPA, there are potential risks to the health of infants [90]. Studies have found that children with non-IgE-mediated and IgE-mediated CMPA (25-60% and 15%, respectively) cross-react with soy proteins [19,246].

Hydroperoxides, which are formed as a result of the breakdown of fatty acids by the lipoxygenase enzyme, cause the taste of raw beans to be felt in soy formulas [247]. In order to eliminate this undesirable taste, processes such as high-temperature vacuum treatment that will inactivate lipoxygenase, boiling in boiling water, hot grinding and adding artificial or natural sweeteners can be applied [218].

Since the heat treatment applied during the preparation of soy milk adversely affects the quality of the final product [218, 248], it is recommended to use non-thermal technologies. On the other hand, Shi and Ren [249] reported that heat treatment increases the digestibility of soy proteins, extends the shelf life of the product, inactivates lipoxygenases and antinutrients, and increases the stability of the emulsion.

It has been reported that calcium-fortified soy beverage is close to cow's milk in terms of macronutrients such as carbohydrates, proteins, and fats [250].

Nut Based Milks

- **Almond Based Formula:** Lipids have the highest share in the composition of almonds with 35%-52%, followed by proteins with 22-25% [251]. While the majority of lipids are unsaturated fatty acids, proteins mostly consist of essential amino acids [252]. The number of micronutrients such as magnesium, calcium, selenium, potassium, phosphorus, zinc, and copper is also high in the composition of almonds, and arabinose in its composition gives it a prebiotic feature [218]. It is known that almonds have positive effects on health. For example, it can reduce the risks of cardiovascular disease, positively affect the level of lipids in the blood, help anaemia, and prevent free radicals and cancer. However, it has an allergenic potential for allergic individuals [251].

Almond milk, which contains bioactive compounds such as fibres, antioxidants and phytosterols, is used as a cow's milk substitute in many countries [225, 252]. Although the nutritional value of almonds is high, their nutritional value decreases when it is made into a beverage [250, 253]. Therefore, it should be supplemented with micronutrients such as vitamin B12 and calcium [229]. Since almond proteins may cause allergic reactions in sensitive individuals [254 255], more in vitro and in vivo studies are needed to safely use almond milk in infants with CMPA.

It is reported that an emulsifier such as lecithin is needed in the preparation of almond milk to produce a stable beverage [256, 257]. The polyunsaturated fatty acids in almonds can cause almond milk to be sensitive to oxidation, resulting in a bitter taste [258]. It has been reported that the heat treatment applied in the production of almond milk may also lead to the oxidation of unsaturated fatty acids and the formation of undesirable sour tastes [259]. Almond milk is thermodynamically unstable due to colloidal substances in its composition [260, 261, 262]. Ultrasound treatment is recommended to stabilize the beverage [263.

- **Hazelnut Based Formula:** Hazelnut is an important food for human nutrition and health due to the compounds such as lipid, carbohydrate, protein, mineral, vitamin, fibre, phenolic compound, tocopherol, squalene and phytosterol in its composition (Table 4) [264]. While triglycerides constitute the majority of the lipids in hazelnut, the rest is composed of fat-soluble vitamins, phytosterol, phospholipids and sphingolipids. About 70% of the amino acids in the hazelnut protein are composed of non-essential amino acids, and the limited amino acid in the hazelnut protein is tryptophan [265].

  Hazelnut-based milks have a unique taste and aroma. Roasting hazelnuts can be applied to obtain different flavours [266]. Gul et al. [267] reported that the homogenization process reduced solid particle sedimentation. Tsai et al. [268] concluded that the amino acid content and physicochemical properties of hazelnut beverages produced by high-pressure applications are better preserved than thermal processing applications. It has been determined that the thermosonication process has a similar effect and can improve the properties of nut beverages such as syneresis and sedimentation index throughout their shelf life [269, 270].

Cereal Based Milks

- **Rice Based Formula:** Rice is a high-energy food with high nutritional value (high protein, minerals, vitamins, and starch) and low lipid content (Table 4) [271, 272, 273]. However, since the bioactive compounds in rice are found in the bran, a significant loss of micronutrients occurs in rice with the milling process. That is, the milling process causes the loss of γ-oryzanol, one of the important bioactive compounds of rice [274].

The limiting essential amino acid in rice, 7% of which is protein, is lysine [273, 275]. If the nutritional quality of rice proteins is increased by supplementing with missing amino acids such as threonine, lysine, carnitine, tryptophan, and taurine, they can be used in baby foods [103]. Rice protein is easily digested, has low allergenicity and is gluten-free, but has poor functional properties due to its low solubility at neutral pH [272, 276, 277]. Rice-based products are a suitable alternative for children with CMPA as they are hypoallergenic [278]. About 95% of the total fatty acids in rice are palmitic (16:0), oleic (18:1) and linoleic (18:2) acids [279, 280]. In addition to being a rich source of B-complex vitamins and vitamin E (α-tocopherol), rice is also rich in potassium, phosphorus, and magnesium [271].

In some Eastern countries, mild sweet-tasting rice beverages are commercially available [281]. Rice extract, which is rich in carbohydrates and soluble in water, has low lipid, protein, mineral substance, and vitamin content [282, 283]. To make rice milk look like cow's milk, flavour enhancers such as vanilla and whole-grain rice syrup are added [282]. The protein characterization of rice milk has not been fully determined [284]. The most important problem in rice milk is its poor emulsion stability. In order to solve this problem caused by high starch content, it is recommended to hydrolyze starch enzymatically with glucosidase or a- and b-amylases [285].

White or brown rice is used in the production of rice milk. Rice, which is liquefied with alpha-amylase enzyme in aqueous medium, is then sugared (saccharification) with beta-amylase and/or glucosidase enzyme. At the end of these processes, milky rice milk is obtained. In order to prevent the formation of undesirable bad tastes, the liquefaction and confectionery stages must be carried out in a short time. Rice milk production can also be accomplished by hot water extraction of ground rice without the use of enzymes [285, 286]. Manfredi et al. [284] identified 158 different proteins in rice milk.

- **Oat Based Formula:** Oat is a grain with high nutritional value due to the fatty acids, amino acids, minerals, vitamins, and dietary fibres it contains. It also contains antioxidants such as ferulic acid, caffeic acid, tocopherol, and avenasterol [287, 288]. Oats are of great interest due to the dietary fibres they contain, especially β-glucan [218]. The b-glucan, which consists of β-D-glucose units with opposite bonds (1, 3) and (1, 4) in oats, gives it high solubility, water binding and viscosity properties [289]. β-glucan has functional properties such as helping prevent colorectal cancer, being beneficial to the digestive system, reducing blood glucose levels, significantly reducing serum concentrations of total lipids and triglycerides and total cholesterol, and increasing the HDL cholesterol fraction [218, 288]. Compared to other grains, oats have a very high lipid content. This can cause problems such as excessive browning and bad taste in toasted products during processing [290]. On the other hand, the lipase enzyme in the structure of oats causes a change in taste in the products and shortens the storage period [291].

  Oat milk prepared by extracting oats in water can be supplemented with calcium and used instead of cow's milk [218, 292]. Since oats contain a high percentage of starch, starch gelatinizes during the heating of the water and oat mixture and increases the viscosity of the gel. To prevent this, starch must be hydrolysed enzymatically [218].

Seed Based Milks

- **Sesame Seed Based Formula:** Sesame seed is a product with strong antioxidant activity as well as containing high protein, oil, and mineral substances [273, 293]. Long-chain saturated and unsaturated fatty acids in sesame seeds provide high nutritional quality [235]. Sesame protein contains abundant sulphur amino acids, while lysine amino acid is limited [294]. The amount of B vitamins and minerals, which are found in high amounts in sesame husk, decreases due to the separation of the husk during the processing of sesame. However, the content of phosphorus, calcium, magnesium, iron, copper, manganese, and zinc is high [235, 294]. Sesamin and sesamolin in the composition of sesame have antioxidant properties and help lower cholesterol [294].

  The roasting process applied in sesame milk production gives the product a roasted taste, while the bleaching process reduces the unwanted enzymatic taste [295]. Sesame based milks are high in protein, lipids, sterols, short-chain saturated fatty acids and calcium. Since the amount of raffinose and stake in sesame-based milks is low, it causes less gas in consumers than soy drinks [293]. Ahmadian-Kouchaksaraei et al. [295] reported that roasting reduces the amount of protein and dry matter in sesame-based milks due to protein denaturation and the release of oil. It reduces the stability of sesame-based milks as the roasting and bleaching processes reveal hydrophobic residues in proteins as a result of denaturation [295, 296]. On the other hand, immersion of seeds in water with sodium bicarbonate increases the stability of sesame-based milks as it provides the formation of hydrophilic lipid-protein complexes due to high pH. [295, 297].

  Since the proteins in sesame are sensitive to heat treatment, they undergo thermal denaturation during the production of sesame-based milk, so modification is required [218, 294]. Quasem et al. [298] reported that while sesame-based milk can tolerate the low temperatures applied in the pasteurization process, it does not tolerate high temperatures in the sterilization process.

  Roasting sesame and soaking it with alkali can reduce the bitterness and chalkiness in its taste, thereby increasing the overall acceptability of sesame-based milk [218]. Sesame based milks can be preferred more than soy beverages because they show lower allergenicity, cause less gas, and have better sensory quality [218, 293].

- **Sunflower Seed Based Formula:** Sunflower seeds contain a high percentage of lipids (Table 4) Most of the high fibre in its composition is located in the shell of the seed [299]. There are phytates and tannins, which are anti-nutrients, in sunflower seeds. While phytates form insoluble complexes with minerals, reducing the bioavailability of these microelements, tannins give astringency to the seed. [300].

The weak gel-forming property of sunflower protein can be improved through proteolysis [301].

Sunflower-based milk obtained at a pH below 6.5 tastes like water, as its protein and dry matter content is reduced. If the pH value is increased above 8.0, polyphenols and chlorogenic acid passing through the seed can cause the beverage to turn green, causing an undesirable green colour, a foul odour, and a bitter taste [302]. Blum et al. [299] reported that the extract obtained from germinated sunflower seeds has low lipid content and calories and does not contain tannins. In order to prevent protein denaturation in the soaking process of the seed for the removal of chlorogenic acid, high temperatures should be avoided, and the process should be completed in a short time. In sunflower-based milks, polysaccharides and/or preservatives should be added to the beverage to prevent gelation during storage [302].

Pseudocereals Based Milks

- **Quinoa Based Formula:** Quinoa is a nutritious food with high protein quality. The amount of limiting essential amino acids cysteine, methionine, and lysine in cereals is quite high in quinoa [303, 299, 305]. Quinoa proteins have a digestibility rate of 80% [306]. The fact that quinoa proteins do not contain gluten has also made it popular in the production of gluten-free foods [307]. Quinoa contains a high amount of carbohydrates, mostly starch (Table 4) [305]. Compared to other cereals, the lipid content is also high [306] and approximately 85% of these lipids are composed of unsaturated fatty acids [303].

In the preparation of quinoa-based milk, the release of starch by using enzymes (α- and β-amylase) is important in terms of being sweet and fluid, as well as nutritionally. Because it contains too much, it is nutritionally important that the beverage is released through the use of enzymes before preparation, amylases are used, and it is important that the beverage be fluid and sweet [308]. Quinoa also contains a higher percentage of minerals than other grains. It contains high levels of magnesium, potassium, calcium, iron, copper, and manganese in its composition and is considered a good source of carotene, vitamin E, folic acid, and vitamin C and B-complex vitamins [306, 307].

The texture of quinoa-based milk is different from cow's milk, and one of the best aspects of this milk is that it can be used as a raw material in various foods such as confectionery, shakes, coffee, pasta [309]. Depending on the type of quinoa, the saponins in its composition can make the taste of quinoa-based milk bitter. To remove this bitter taste, processes such as washing and peeling are applied [304]. The viscosity of quinoa-based milk is quite high compared to other beverages.
Although pea, lupine, coconut, and hemp-based beverages are also produced in addition to the plant-based milks mentioned above, it is stated that these beverages are not suitable for children under the age of two [180].

IV. CONCLUSION

Cow's milk and dairy products are one of the 8 main allergens. Therefore, CMPA is the most common allergy among young children and is responsible for anaphylaxis reactions. Cow's milk formulas developed with technological processes, other mammalian milks or plant-based milks that children with CMPA can consume as an alternative to cow's milk are recommended. Among these milks, it is stated that extensively hydrolysed cow's milk protein-based formulas and amino acid-based formulas from hydrolyzed cow's milk and rice-based formulas from plant-based milks are much better options and are recommended as the first choice.

Other mammalian milks (ewe, goat, donkey, mare, and camel milk) are considered to be more suitable alternatives for children older than 1 year with severe CMPA. However, it should be kept in mind that proteins in the milk of other mammalian species may cross-react with cow's milk proteins and carry risks. Especially consumption of ewe's and goat's milk is not recommended for allergic children due to the strong cross-reaction of the proteins of these milks with cow's milk proteins. On the other hand, it has been determined that these milks may be suitable alternative protein sources for children with CMPA because the proteins in donkey's, mare's and camel's milk cross-react with cow's milk proteins and have low sequence identity. Especially camel's milk, which does not contain β-LG protein; is seen as a promising option for children allergic to β-LG. If horse milk is to be taken into the diet, attention should be paid to enriching it with unsaturated fatty acids or meeting the insufficient components with other nutrients, considering that it has low iron and lipid content and gives less energy. Therefore, horse milk formulas should not be used alone, but as a supplement to a balanced diet. Camel milk is recommended as a suitable alternative because its proteins are different from cow's milk proteins and because of its high nutritional value. However, more research is needed on the allergenicity of camel milk proteins.

Since the nutritional quality of plant-based milk is lower than cow's milk, these milks should be enriched if they are to be used instead of cow's milk. On the other hand, due to the lack of flavour and low general acceptability in plant-based milks, more studies are needed to develop these formulas. Future studies should be conducted to develop formulas that replace cow's milk for children with CMPA.

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