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Alternative Milk Options for Infants with Cow's Milk Allergy: A Systematic Review of Goat's Milk, Plant-Based Milk, and Partially Hydrolyzed Protein

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Abstract
Introduction: *Cow's milk allergy (CMA) is the most common food allergy occurring in the first year of life. Restriction of cow's milk and dairy products results in decreased macro- and micronutrient intake, especially in infants who are not breastfed. Therefore, alternative milk supplements for supplemental nutrition in CMA must be considered.* ***Methods:*** *This systematic review used PRISMA guidelines with the PICO search strategy, focusing on RCTs, clinical trials, and observational studies. A comprehensive search was conducted to obtain articles published in English between 2010 and 2025 using ScienceDirect, PubMed, SagePub, and Scopus.* ***Result and Discission:*** *Results A total of 2010 publications were retrieved using relevant search terms. After a rigorous three-stage review, nine studies were selected based on inclusion criteria and deemed suitable for in-depth analysis. These studies addressed tolerance and allergic reactions or cross-reactivity following administration of goat's milk, soy isolate, rice isolate, and partially hydrolyzed formula.* ***Conclusion:*** *In infants with CMA, goat's milk can trigger cross-reactivity. Partially hydrolyzed formulas can be an option for oral food challenges to assess tolerance. Plant-based formulas, particularly rice isolate, are the best choice, especially for those with non-severe CMA and CMA who cannot tolerate extensively hydrolyzed and amino acid-containing formulas.*

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Introduction

Cow's milk allergy (CMA) is a reproducible hypersensitivity reaction that occurs after consuming a food allergen. This condition most often occurs in the first year of life, with a prevalence of 2–6% and decreasing with age (Emmert, Lendvai-Emmert, Eklics, Prémusz, & Tóth, 2023). In studies using self-reported criteria, the prevalence of CMA in Indonesia ranges from 1.2% to 17%. (Paquete et al., 2022). CMA can elicit different immune responses depending on its subtype: IgE-mediated (type I hypersensitivity reaction) and non-IgE-mediated (type III and IV hypersensitivity reactions). IgE-mediated CMA exhibits a response within minutes to two hours, with symptoms including urticaria, pruritus, swelling, nausea and/or vomiting, abdominal pain, wheezing, systemic reactions, and even anaphylaxis.(Edwards & Younus, 2024). Non-IgE-mediated symptoms typically appear within hours to several days, including food protein-induced enterocolitis syndrome, food protein-induced enteropathy, and food protein-induced allergic protocolitis. 1 Cow's milk contains more than 20 protein fractions, with significant allergens being casein protein (80%; α1, β2, β-, β-casein) and whey protein (20%; β-lactalbumin and β-lactoglobulin). The casein protein content in milk, particularly α1-casein, is the primary allergen in CMA and plays a role in the development of persistent allergies

The primary management of children with CMA is to eliminate dairy products. However, insufficient intake of cow's milk and dairy products is associated with decreased macro- and micronutrient intake, which is associated with delayed growth and development (Gibson, Stanley, Agarwal, Groetch, & Bunyavanich, 2021; Lajnaf et al., 2023). In situations where breastfeeding is not possible, replacement with formula should be considered. Nutritional options for CMA include extensively hydrolyzed formula (EHF) and amino acid-rich formula (AAF), but these formulas have the disadvantage of being expensive and not widely available. Therefore, consideration should be given to mammalian milks other than goat's milk, plant-based milks, and partially hydrolyzed milks as a second-line option for infants with CMA (Verduci et al., 2020). The use of alternative milks, such as goat's milk, is considered a potential option for children with CMA due to its lower α-caseine content, although some studies have shown differences in tolerance. Different protein fractions in plant-based milks may be considered a promising option for CMA. 6 Partially hydrolyzed cow's milk protein-based formula (PHF) contains peptides with a lower molecular weight of 1.3 (3-10 kDa), which is thought to induce oral tolerance without causing sensitization (Lajnaf et al., 2023; Vandenplas, De Greef, Hauser, & Group, 2014).

Against this background, this systematic review aims to systematically assess the use of goat's milk, rice milk, soy milk, and PHF milk as alternative nutritional supplements for children with CMA. This review aims to provide evidence-based guidelines, characterized by reduced allergic reactions and improved markers of allergy-specific immune responses when using alternative milks.

Method

This study is a literature review through a systematic search conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy was developed using the Population, Intervention, Comparator, Outcome (PICO) framework. A search strategy was carefully designed to identify relevant studies for this systematic review. Researchers used databases such as

PubMed, Science Direct, SCOPUS, and SagePub to search for randomized controlled trials (RCTs), clinical trials, and observational studies from 2010 to 2025. The search terms used included: ("infant" OR "baby" OR "child" OR "1-12 months") AND ("cow milk allergy" OR "CMA" OR "CMPA" OR "milk protein allergy") AND ("goat milk" OR "plant-based milk" OR "rice milk" OR "soy milk" OR "partially hydrolyzed protein milk"). Search terms were tailored for each database to optimize record retrieval. The data collection process involved a thorough initial screening to evaluate each article systematically.

This structured approach ensured the identification of consistent and meaningful patterns across the literature, focusing only on studies directly relevant to the research question. The data were collected in the form of full-text articles published in English. All selected studies were ensured to meet the established inclusion criteria. The evaluation process also involved a detailed assessment of the study title, author names, publication date, research location, and methodology used to provide a basis for drawing credible, evidence-based conclusions.

Result and Discussion

1. Result

The research began with a systematic search of leading academic databases, including ScienceDirect, PubMed, Scopus, and SagePub, to identify studies relevant to this review. A rigorous three-stage screening process was applied to screen and select the most suitable studies, ultimately resulting in nine articles that met the predetermined inclusion criteria. The selected studies were then comprehensively analyzed, with key themes and key findings extracted for further in-depth examination. To ensure clarity and facilitate the presentation of the results, the findings are summarized in Table 1, which presents a concise and organized overview of the analyzed data.

Table 1
The Literature Included in This Study

Author	Method	Sample	Milk Formula	Result
(Reche et al., 2010)	Randomized control trial	92 babies	Hydrolyzed rice protein formula	Rice protein-based formulas had similar tolerability to standard EHF. All infants had negative skin prick test results for both rice extract and rice protein formulas. No increase in IgE was observed after administration of these formulas. Further evaluation revealed tolerance to cow's milk at 12 months (18 samples), 18 months (26 samples), and 24 months (31 samples).
(Nicolaou et al., 2022)	Multicenter double-blinded randomized control trial	331 babies	Partially hydrolyzed formula	Studies show a tendency to reduce the incidence or development of Atopic Dermatitis (CMA) in infants at high risk of allergies who are not breastfed, making PHF a preventative option for Atopic Dermatitis (CMA) in infants. Whey-based formula can reduce the incidence of atopic dermatitis in infants with ATOPIC Dermatitis (CMA).
(Vandenplas et al., 2014)	Clinical trial	31 babies	Extensive hydrolyzed	After formula administration, the incidence of bowel disorders (hard or

			rice protein formula	watery stools) decreased from 51.3% to 10.8%. Infants with CMA tolerated the formula well, with statistically significant improvements in urticaria and eczema on the head, neck, and trunk.
(Vandenplas et al., 2019)	Clinical trial	38 babies	Extensive hydrolyzed rice protein formula	Research shows that more than 90% of infants with CMA tolerate rice protein formula. Symptom-based scores at 1, 3, and 6 months of administration showed improvement, including stool consistency, absence of urticaria, eczema, and respiratory symptoms
(Setiabudiawan et al., 2021)	Multi-site clinical trial	53 babies	Soy-based infant formula	At the beginning of the study, 8% of infants did not tolerate soy formula well. At the end of the study, an evaluation to assess atopic dermatitis (SCORAD) was conducted and found a decrease in the incidence of mild atopic dermatitis with no moderate or severe cases. Based on the symptom-based clinical score, no infants were found to be likely related/at risk after soy milk administration from weeks 4 to 24.
(Lowe et al., 2011)	Randomized control trial	412 babies	Partially hydrolyzed formula dan soy formula	There was no evidence to suggest a reduction in allergic manifestations in infants fed PHF formula or soy formula compared to conventional formula. There was no reduction in the risk of skin prick test reactivation or childhood allergic disease.
(Gunaydin et al., 2021)	Retrospective cross-sectional	66 babies	Goat milk	While 73% of infants with CMA were able to consume goat's milk, the study showed a significant increase in the IgE immune response biomarker after administering goat's milk to infants with CMA. Although the incidence of respiratory symptoms, urticaria, angioedema, and gastrointestinal disorders was lower when given goat's milk, allergic reactions due to cross-reactivity were still observed.
(Sancaklı, Yenigün, & Tuncel, 2019)	Clinical trial	53 babies	Goat milk	Fifteen infants with CMA tested positive on early skin prick tests (10 infants) and atopy patch tests (5 infants). Ten of these tested positive after being given goat's milk as an oral food challenge (7 positive on skin prick tests and 3 positive on atopy patch tests).
(Santi, Juffrie, & Sumadiono, 2012)	Case-control	43 babies	Soy-based Formula	At 6 weeks follow-up, no soy protein sensitization was found, with negative skin prick test results in either the case group (infants with CMA) or the control group (infants without CMA).

2. Discussion

CMA is the most common allergic presentation in early childhood, with an estimated incidence of CMA of 2% in infants and 4.5% in the pediatric population. Cow's milk contains various protein fractions, consisting of 80% casein protein and 20% whey protein. Casein is the main allergen, encompassing four isoforms: α-casein, α-casein, β-casein, and γ-casein.18 Management of CMA includes avoidance of cow's milk and foods containing cow's milk protein through individualized strategies (Meyer et al., 2023; Venter et al., 2024) The WHO recommends continuing exclusive breastfeeding for the first six months of life. In infants with CMA, breastfeeding restriction is not necessary, but mothers should avoid cow's milk during breastfeeding (Venter et al., 2024). For infants who are not breastfeeding or whose breast milk production is insufficient, cow's milk formula is used for supplemental nutritional therapy. Therefore, alternative milk options should be considered in infants with CMA.

Hydrolyzed formulas have a nutritional profile comparable to standard cow's milk formulas, although they have been enzymatically treated with hydrolases to produce more digestible and less allergenic peptides. Depending on the degree of hydrolysis and the molecular weight of the resulting peptides, hydrolyzed formulas can be classified as PHF, which contains peptides of 3–10 kDa, or EHF, which consists of >90% peptides with a molecular weight of <3 kDa. PHF has been reported to be effective in supporting adequate growth and reducing the risk of atopic dermatitis in infants at high risk for allergies (Matsubara et al., 2023) Although not as effective as EHF, studies in older children have shown a substantial reduction in PHF reactivity in children with CMA, and PHF tolerance has been found to be achieved in 40–75% of children. (Inuo et al., 2019; Matsubara et al., 2023).

Research conducted by randomized controlled trials (RCTs) in infants with CMA has shown differences in outcomes after PHF administration. A 2011 study involving 412 infants showed no evidence of a reduction in allergic manifestations or a reduced risk of allergic reactivation compared with conventional formula (Nicolaou et al., 2022). Disparate findings were obtained in a smaller, multicenter study involving 331 infants in 2022, which showed that administering whey-based PHF (PHF-W) reduced the incidence of atopic dermatitis in infants with AML compared with conventional formula (Nicolaou et al., 2022). The difference in results may be due to the lack of a strict assessment of AML as IgE-mediated or non-IgE-mediated, thus allowing for differences in response to PHF administration. From a regulatory perspective, PHF-W meets all nutritional requirements and can be considered an alternative to conventional cow's milk formula with intact proteins for all non-breastfed infants. Therefore, the use of PHF-W for non-breastfed infants who are not at risk can be considered and can be an option for reintroduction or oral food challenge in infants with CMA (Vandenplas et al., 2019).

In the population with CMA, providing other mammalian milks as an alternative has been controversial due to the structural similarity of the proteins. This makes it possible for cross-reactions to occur when giving other mammalian milks to children with CMA (Williams, Erdle, Cochrane, Wingate, & Hildebrand, 2023). Goat's milk has long been considered a substitute in the CMA population. This is supported by preclinical studies showing goat's milk to be less allergenic than cow's milk due to its lower α-1-casein content. However, studies have shown a high degree of homology between goat's milk proteins and cow's milk proteins, which is a consideration for goat's milk restriction in infants with CMA (Zhao et al., 2023)

Table 2
Composition and homology of goat milk proteins compared to cow milk proteins

Milk protein	Cow's milk	Goat milk	Homology
αs1-casein	27%	1%	89.7%
αs2-casein	8%	16%	90.1%
β-casein	34%	51%	91%
k-casein	9%	8%	59.5%
β-lactoglobulin	16%	17%	88%
α-lactobumin	4%	6%	92%

Clinical trials and cross-sectional studies in 2019 and 2021 demonstrated cross-reactivity to goat's milk in infants diagnosed with CMA. Although the incidence of CMA symptoms, such as respiratory symptoms, urticaria, angioedema, and gastrointestinal disturbances, was lower in infants fed goat's milk, there was a significant increase in IgE biomarkers and positive results on skin prick tests and atopy patch tests (Gunaydin et al., 2021; Sancaklı et al., 2019). This is consistent with previous studies in larger child populations that demonstrated cross-reactivity and a lack of tolerance to goat's milk in children with CMA, particularly IgE-mediated CMA. Plant-based formula is an alternative option because its protein content is very different from cow's milk-derived formula, thus allowing for tolerance in children with CMA. Clinical studies (RCTs and clinical trials) using infants with CMA have demonstrated tolerance to rice protein formula similar to standard EHF via cow's milk derivatives. A 2010 study showed no increase in immune response biomarkers and negative skin prick test results after administering rice extract and rice protein formula to infants with CMA (Reche et al., 2010).

A 2014 study showed improvement in clinical symptoms of CMA after the administration of rice formula, as indicated by improved bowel movements and a reduction in skin reactions (urticaria and eczema). In addition to rice formula, soy formula in infants with CMA also showed good results. A 2012 study showed no soy protein sensitization, as indicated by negative skin prick test results, after 6 weeks of soy protein administration in infants with CMA (Santi et al., 2012). Although some infants did not tolerate soy formula well (8% at the beginning of the study), a 2021 study also showed a decrease in the incidence of mild atopic dermatitis and no moderate or severe cases after the introduction of soy milk. Administration of soy formula until week 24 did not indicate any infants at risk of allergic reactivation based on a scoring system. Soy-based formulas are soy protein isolates derived from soybean components. Soy formulas are tailored to the nutritional needs of infants and children, as per regulatory criteria. In rice-based formulas, the final product contains hydrolyzed protein with additional components tailored to the specific needs of infants and children (Brusati, Baroni, Rizzo, Giampieri, & Battino, 2023).

Table 3
Energy and macronutrient composition of plant-based and cow's milk. 18.26

/100 mL	Energy (Kcal)	Protein (g)	Fat (g)	Carbohydrate (g)
Cow	60	3.3	3.3	4.6
Soy	44	3.3	2.0	3.0
Rice	57	0.2	1.0	12.0

The 2023 DRACMA guidelines state that hydrolyzed rice-based infant formula is the primary treatment option for infants with IgE-mediated or non-IgE-mediated CMA if breastfeeding is not available. Furthermore, soy-based infant formula is a last resort. Despite its hypoallergenic nature, alternative plant-based formulas do not provide adequate nutritional support, especially for infants under 1 year of age, as they can lead to growth disorders, malnutrition, electrolyte disturbances, and nutritional deficiencies.15

Conclusion

Cow's milk allergy is the most common food allergy presentation in children in the first year of life. Restriction of cow's milk, especially in infants with CMA who are not exclusively breastfed, is a consideration, necessitating the provision of hypoallergenic alternative milks. Goat's milk is not an alternative option for infants with CMA due to its high protein homology, which can trigger cross-reactivity. Partially hydrolyzed formula can be an option for reintroduction and oral food challenges in infants with CMA to assess tolerance. Plant-based formula is the best alternative for CMA, especially in the population who are not exclusively breastfed. Soy formula has a higher protein content, making rice formula the best choice for infants with CMA with the lowest likelihood of cross-reactivity, especially in non-severe CMA and CMA intolerant to EHF and AAF.

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