

# Allergy Prevention Mechanisms of Human Milk Proteomes in Infants: A Scoping Review

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## ABSTRACT

**Background:** There has been an evident rise in global prevalence of allergic diseases, such as food allergies, eczema, asthma, and allergic rhinitis but most notably in infants in recent times. Human milk contains diverse bioactive compounds that modulate immunity and protect against allergies. Of the main bioactive components of human milk, the human milk proteome, a broad spectrum of proteins as well as peptides has emerged as a key agent in modifying allergic reactions. This study aims to explore the relationship between the human milk proteome and the development of allergies in infants, focusing on their mechanisms in preventing allergen sensitivity. **Methods:** A comprehensive search of peer-reviewed articles published between 2015-2025 was conducted in PubMed, Scopus, and ScienceDirect using the keywords: (“human milk” OR “breast milk”) AND (“proteome” OR “proteins”) AND (“allergy” OR “hypersensitivity”) AND (“infant” OR “newborn”). Of 533 articles retrieved, 26 passed screening, and 4 met the inclusion criteria, as illustrated in the PRISMA-ScR flow diagram. **Results:** It was found that there are seven proteomes of human milk that contain immunological components which are IgG, secretory IgA (SIgA), Vitronectin, CD81, C4A, IgG4 and interleukin-10 (IL-10). These components are involved in different mechanisms that prevent sensitivity to allergens such as transferring passive immunity that blocks allergen sensitization and promote immune tolerance by modulating inflammatory responses. The types of allergies included in this study are food allergies, atopic dermatitis, allergic rhinitis, asthma, allergic sensitization, eczema and respiratory allergies such as pollen allergies. **Conclusion:** The study highlights the imperative role of human milk proteomes such as immunoglobulins, SIgA, and IL-10 in lowering the risk of developing allergic illnesses like asthma, eczema, and allergic rhinitis by inhibiting allergic sensitization, preventing infections, and triggering a synergistic immune response. Further studies will be needed to investigate the synergistic roles of these bioactive components and their sustained effects on allergy prevention to improve global public health.

## Keywords:

human milk; proteomes; allergy; infants

## INTRODUCTION

The increasing prevalence of allergies, including food allergies, eczema, allergic rhinitis, and asthma, highlights the need for a deeper understanding of early-life factors influencing immune development. In accordance with the 2011 White Book on Allergy, the incidence of allergic disorders is experiencing a significant increase on a global scale, encompassing both industrialized and emerging nations, with the prevalence rates of asthma fluctuating between 1% and 20%, allergic rhinitis ranging from 1% to 18%, and dermatological allergies varying from 2% to 10% across diverse demographic groups (Gutowska-Ślesik *et al.*, 2023). More recent global reports from the Global Allergy and Asthma European Network (GA<sup>2</sup>LEN), the World Allergy Organization (WAO), and analyses from the Global Burden of Disease (GBD 2021) confirm that allergic diseases continue to pose a major public health challenge. The GBD 2021 estimates indicated that approximately 260 million people were affected by asthma and 129 million by atopic dermatitis worldwide in 2021, with projections showing further increases by 2050 (Oh *et al.*, 2025). The growing prevalence of allergies is particularly noticeable in children, who have been affected most by this trend for the last two decades. Allergy prevention targets the prevention of the development of allergic diseases and the reduction of the risk of its occurrence. Allergy prevention entails measures that are directed at reducing exposure to allergens and enhancing the immune system's capacity to distinguish between dangerous and safe agents. Allergy prevention is particularly influenced by determinants that occur in early life, including breastfeeding with a

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modulating effect on the immune system, which lowers the risk of allergic sensitization (Ballard & Morrow, 2013; ASCIA, 2020). Human milk is widely acknowledged for its protective role against allergies, attributed to its rich composition of bioactive components (Ballard & Morrow, 2013).

Among these, it is the human milk proteome which is the most dynamic collection of proteins and peptides that is emphasized due to its immunomodulatory characteristics. These proteomes assist in the maturation of the infant's immune response, foster tolerance towards allergens and modify gut microbiomes. For example, Kull *et al.* (2010) showed that the risk of allergic sensitization and asthma in children who were exclusively breastfed for at least four months was lower than in those who were breastfed for less than four months.

The human milk proteome includes nutritional proteins such as caseins and whey proteins, immunological proteins like lactoferrin, lysozyme, and secretory immunoglobulin A (SIgA), as well as bioactive peptides that influence immune regulation. According to Zhu and Dingess (2019), this proteomic diversity allows human milk to adapt to the changing needs of the infant throughout lactation, providing essential support for growth and development. These components are thought to play a significant role in fostering immune tolerance, a process by which the infant's immune system learns to distinguish between harmful and harmless antigens.

Despite evidence suggesting a protective effect of breastfeeding on allergy risk, inconsistencies in study findings and limited understanding of the role of specific human milk proteomes present a significant knowledge gap. Clarifying these mechanisms is crucial to developing targeted nutritional strategies that could mitigate allergy risk in infants. This study aims to explore the relationship between the human milk proteome and the prevention of allergies in infants, with a focus on identifying specific proteomes and their mechanisms of action in preventing allergen sensitivity.

## METHODOLOGY

This study employed a scoping review methodology to investigate the role of the human milk proteome in the prevention of allergies in infants. Scoping reviews were suitable for this purpose as they enabled the comprehensive mapping of diverse literature, methodologies and findings across broad research areas. This approach was guided by the framework of Arksey and O'Malley (2005) and adhered to the PRISMA-ScR checklist to ensure clear and thorough reporting (Tricco *et al.*,

2018). This design allowed for a detailed analysis of existing evidence, identifying mechanisms, gaps, and potential clinical applications.

### Stage 1: Identify the Research Questions

The research questions identified which are 1) Which proteomes in human milk contribute to prevention of allergen sensitivity in infants? and 2) What are the mechanisms of action of the proteomes in human milk in preventing allergen sensitivity in infants? These research questions were used to guide the search strategy and were further evaluated using the eligibility criteria to choose the most relevant articles for inclusion in this scoping review.

### Stage 2: Identify Relevant Studies

Research articles were collected from a number of prominent databases, including PubMed, Scopus, and ScienceDirect. The search for articles was limited to those published in the past ten years, i.e., 2015 to 2025, to guarantee inclusion of the most current and pertinent data on the subject. Search keywords were drawn from subject-related keywords of the human milk proteome and its role in immune tolerance and allergy prevention in infants. Boolean operators such as "AND," "OR," and "NOT" were employed to combine and exclude terms to restrict the search for better retrieval and capture of relevant articles. These operators were applied to restrict the search to articles that met the inclusion criteria of human milk proteome and infant allergies. For example, the following phrases were used: (((("human milk" OR "breast milk") AND ("proteome" OR "proteins") AND ("allergy" OR "hypersensitivity") AND ("infant" OR "newborn")))). By utilizing these operators, the search was optimized to identify the most relevant studies while avoiding non-relevant articles.

### Stage 3: Study Selection

The following studies were included if they met the criteria: (1) fulfill both objectives, (2) publications from the last 10 years, (3) articles written in English, and (4) full-text articles. Studies were excluded if they were unpublished hand-searched, grey literature, review articles, book chapters, conference abstracts, letters or if they fulfilled only one objective.

### Stage 4: Charting the Data

The data were charted beginning with duplicate citations removed for independent title, abstract, and full-text

review based on the inclusion criteria. Titles and abstracts were screened independently and in parallel for potential inclusion. Potentially eligible sources were retrieved in full text. Full-text sources were screened independently against the inclusion criteria. The results of the search and inclusion of the study were reported in full in the final scoping review and summarized in a PRISMA-ScR flow diagram as shown below in **Figure 1**.

### Stage 5: Collating, Summarizing, and Reporting Result

This stage describes the key steps of the review process. First, the study characteristics were summarized, including the author, year of publication, study title, and journal source. Next, the methods used in each study were outlined, covering the study design, research objectives, and approaches applied. Finally, the findings were synthesized according to the objectives of this review, highlighting the human milk proteomes identified in the selected studies, their mechanisms of action in preventing infant allergies, and the types of allergies discussed. An informal quality appraisal was conducted to provide a clearer understanding of the robustness and validity of the included studies. It involved assessing the clarity of the study's purpose, the appropriateness of its design, and potential sources of bias. Although no standardized tool or ranking system was used, this process allowed for contextualization of the findings and the identification of research gaps, which may inform future high-quality studies. Data extraction through this process was helpful in addressing the objectives and research questions of the scoping review. These tables provided a descriptive summary of the findings and collectively created a more comprehensive picture of the study.

## RESULTS

### Study Characteristics

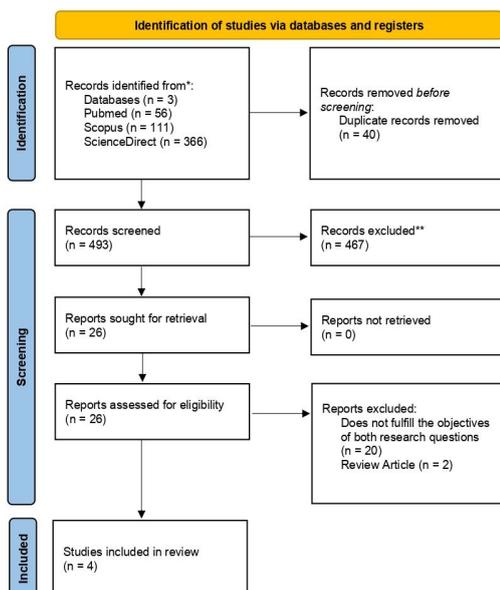
The selected articles were experimental research studies. This review included findings from several journals: Lupinek *et al.* (2019) in *The Journal of Allergy and Clinical Immunology*, Donald *et al.* (2024) in *Cell Reports*, Jiang *et al.* (2021) in *Molecular Nutrition & Food Research*, and Manti *et al.* (2016) in *Immunobiology*. All of the studies used human breast milk, although one employed a mouse model. Despite using different approaches, all studies confirmed the beneficial role of the human milk proteome in allergy prevention.

### Human Milk Proteome Components and Their Mechanisms in Preventing Allergy

The included studies focused on specific components of human milk that contribute to allergy prevention. Donald *et al.* (2024) demonstrated that secretory IgA (sIgA) regulates the gut microbiome and prevents asthma. Jiang *et al.* (2021) identified multi-omics components such as vitronectin and CD81 that support immune development and reduce allergy risks. Lupinek *et al.* (2019) found that allergen-specific IgG in breast milk protects against respiratory and food allergies, while Manti *et al.* (2016) reported that milk-derived interleukin-10 (IL-10) promotes immune tolerance and alleviates cow's-milk-protein allergy. **Table 1** summarizes the mechanisms of action of these key proteomes in preventing specific types of allergies. This table is important for illustrating how each proteome component functions in relation to different allergic conditions. **Table 2** presents a consolidated summary of the main proteomes identified and their mechanisms of action. It provides a concise comparison that highlights how multiple human-milk proteins contribute synergistically to immune tolerance and reduced allergy risk in infants.

## DISCUSSION

This study aimed to explore the role of proteomes present in human milk in preventing allergen sensitivity in infants. Specifically, the study was focused on identifying the specific proteomes of human milk involved in infant allergy prevention and identifying how these proteomes function to prevent allergen sensitivity. From the findings, human milk contains a wide range of bioactive molecules like immunoglobulins, sIgA, and IL-10, which are all crucial for ensuring the integrity of the immune system and causing resistance to allergies. This present scoping review presents important findings on the role of the human milk proteome in reducing inflammation, and gut health,



**Figure 1:** PRISMA ScR flow diagram

**Table 1: Mechanisms of Proteomes in Preventing Allergies**

Author & Year	Mechanism of Action	Type of Allergy
Donald <i>et al.</i> , 2024	Breast milk-derived secretory IgA (sIgA) modulates the neonatal gut microbiota by blocking immunogenic bacteria colonization (segmented filamentous bacteria, SFB), preventing overactive Th17 immune responses and reducing asthma susceptibility.	Asthma
Jiang <i>et al.</i> , 2021	Human milk proteome as factor 2 influence infant growth and susceptibility to allergy through interactions with infant metabolism and immune development. The multi-omics components co-regulate infant health outcomes.	Eczema, Asthma, Rhinitis, and Atopic Dermatitis
Lupinek <i>et al.</i> , 2019	Mother-specific allergen-specific IgG antibodies are transmitted through placenta and breast milk to infant and transfer passive immunity that blocks allergen sensitization and reduces child IgE-mediated allergy induction.	Respiratory Allergies like pollens
Manti <i>et al.</i> , 2016	Breastfeeding provides immunologically active components like IL-10, which promotes immune tolerance by modulating inflammatory responses (Th1/Th2 balance), resulting in reduced severity of allergic symptoms and improved disease outcome.	Cow's Milk Protein Allergy (CMPA)

**Table 2: Summary of Key Findings**

Proteomes	Mechanism of Action
Secretory IgA (sIgA)	Blocks gut colonization by immunogenic bacteria; suppresses Th17 responses
Vitronectin, CD81, C4A, IgG4	<ul style="list-style-type: none"> <li>Interact with metabolism and immune signals via multi-omics pathways</li> <li>Influence growth and allergy susceptibility</li> </ul>
IgG	<ul style="list-style-type: none"> <li>Transfers maternal allergen-specific IgG; prevents IgE sensitization</li> <li>Passive immunity, prevents allergy onset</li> </ul>
IL-10	<ul style="list-style-type: none"> <li>Balances Th1/Th2 responses; suppresses inflammation</li> <li>Promotes immune tolerance</li> </ul>

particularly in preventing allergies in infants. This review synthesizes such findings, identifies their mechanisms of action, and affirms the need for increased research to enhance our understanding of the interaction between human milk proteomes and the immune system.

**Mechanisms of Proteomes in Preventing Allergies**

The proteomes that can prevent allergies are proven by collecting data from research articles. Firstly, in a study by Donald *et al.* (2024) stated that sIgA organizes infant gut microbial populations by adhering to specific bacteria. It limits colonization by certain immunogenic bacteria such as Segmented Filamentous Bacteria (SFB), which if uncontrolled, could overstimulate the immune system. By controlling bacterial colonization, sIgA prevents premature or excessive immune stimulation. Without sIgA, bacteria such as SFB overgrow and are in close contact with the gut lining. This bloom results in early and increased activation of Th17 cells, which are immune cells involved in inflammation. Increased Th17 responses are involved in allergic inflammation and asthma. sIgA controls excessive expansion of pro-inflammatory immune-driving bacteria during early life. This balances the types of immune cells, including regulatory T cells (Tregs) that promote allergen tolerance. This is supported by the findings of Rahman *et al.* (2023), which emphasized that sIgA is beneficial for mucosal immunity and regulates

innate and adaptive immunity and, by extension, dampens allergic inflammation risk. These findings also indicate immunological importance of SIgA for stabilizing milieu of guts and preventing immune hyperresponsiveness. Selective arranging within gut microbes through SIgA follows intricate molecular mechanisms revealed within the KEGG pathway hsa04672 (Intestinal Immune Network for IgA Production), where SIgA is secreted in an active form from plasma cells within mucosal tissues, then adheres with help through the polymeric immunoglobulin receptor (pIgR). In a selective manner, the attachment denotes SIgA stringently regulates microbial populations, where good species are free towards dominating with potentially pro-inflammatory ones, for example, SFB, kept in line. In the absence of these, as in the case for the Th17 cell differentiation pathway (hsa04659), SFB overgrowth can potentially initiate IL-6, TGF- $\beta$  mediated Th17 polarization, heading towards inflammatory cytokine production like IL-17A, IL-22. Chronic allergic inflammation results from pro-inflammatory cytokines, with a break in immune tolerance. Also, SIgA interaction with Tregs, as in the case for the TGF-beta signaling pathway (hsa04350), initiates IL-10, TGF- $\beta$  secretion, heading towards a state of anergy/immunological suppression, Th1/Th2/Th17 balance. In short, SIgA, besides downregulating dysbiosis-derived inflammation, also imposes an early tolerant, homeostatic immunologic environment, with a decrease in risk for allergy through multiple complementary immunoregulatory mechanisms.

Moreover, in the study by Jiang *et al.* (2021), key proteomes such as Vitronectin, CD81, Complement C4A, Immunoglobulin  $\gamma$ 4 (IgG4) are categorized as factor 2. Vitronectin is involved in cell adhesion and immune regulation. CD81 involved immune cell signaling and regulation. Complement C4A is a part of the complement system, and it supports immune defense and pathogen removal. Immunoglobulin  $\gamma$ 4 an antibody subunit important to immune response. Factor 2 is inversely associated with  $\alpha$ s1-casein, a well-known cow milk allergenic protein. Samples of Factor 2 milk have reduced levels of the major milk allergen  $\alpha$ s1-casein. Lower exposure to the allergen, lowers the risk of sensitization and allergy in infants like eczema, asthma, rhinitis, and atopic dermatitis. The combination of immunoregulatory proteins supports the development of immune tolerance, meaning the infant's immune system learns to recognize harmless antigens without overreacting. Statistically, higher levels of Factor 2 proteome are linked with a 35% lower risk for infant allergy. These are supplemented with KEGG pathway integrations. In Complement and Coagulation Cascades (hsa04610), Vitronectin action stabilizes interaction with complement components with a modulatory influence on inflammatory activity. C4A also

takes part in immune tolerance through processing and clearance of immune complexes. In Cell Adhesion Molecules (CAMs) (hsa04514), CD81 participates in tetraspan-enriched microdomains, modulating immune cell adhesion and immune cell signaling. CD81 and Vitronectin are also common in Antigen Processing and Presentation (hsa04612), with regulated antigen recognition and immune regulation being supplied. IgG4, although cataloged for no given KEGG pathway, has shown an action as a "blocking antibody" through competitive inhibition of IgE attachment and an inhibitory influence on IgE-induced allergic reaction (Platts-Mills *et al.*, 2021). Legrand (2016) also mentioned C4A immune-modulatory effect, which has a specific influence in tolerance induction at early developmental stages in immunity.

Besides that, the study by Lupinek *et al.* (2019) shows that mothers form specific IgG antibodies into ubiquitous allergens during pregnancy, and they transfer these to their babies through the placenta and in breast milk. The maternal IgG antibodies protect the babies by inhibiting allergens from provoking allergic reactions. As an example, allergens like timothy grass pollen (Phl p 1), birch pollen (Bet v 1), cat allergen (Fel d 1), wasp venom (Ves v 5), and common food allergens like peanut (Ara h 1), cow's milk (Bos d 5), egg (Gal d 1), and wheat (Tri a 36) were included in the study. If mothers have high levels of IgG antibodies against these allergens, their children are less likely to become allergically sensitized (IgE response) to the same allergens by the time they are five years old. The protective effect is because maternal IgG can neutralize allergens or remove them before they can trigger an allergic reaction. The babies start making their own IgG antibodies around six months, but the maternal IgG shields them during the initial six months when their immune system is not developed yet. In the KEGG pathway Fc gamma R-mediated phagocytosis panel (hsa04666), it is demonstrated, where attachment of IgG-allergen complexes through Fc $\gamma$  receptors on leukocytes with subsequent clearance through phagocytosis inhibits inflammation. In the Antigen Processing and Presentation panel panel (hsa04612), IgG determines antigen presentation toward a tolerogenic direction, with a hope for immune tolerance. Also, in the Complement and Coagulation Cascades panel panel (hsa04610), IgG activates the classical complement system for elimination of immune complexes. In the processes, there are descriptions where high maternal IgG level, especially above 30 ISU-G, results in protection for allergic sensitization in childhood. It is also an ongoing protection demonstrated by Ballard and Morrow (2013), where there were descriptions for how maternal IgG gives early protection for infection. Rajani *et al.* (2018) also showed a long-term function for maternal IgG in infants, with a lower

risk for allergic disease like eczema, also for asthma. In total, there are clear results demonstrating a clear proof for how maternal IgG, both through passive transfer, also through molecular immunity mechanisms, plays a crucial role in providing for the infant's first environment for immunity, with protection for developing an allergic condition.

Lastly, Manti *et al.* (2016) provided evidence that breast milk anti-inflammatory cytokine interleukin-10 (IL-10) plays a key function in controlling allergic reactions in infants. Breastfeeding CMPA babies had higher serum IL-10 levels than non-breastfeeding CMPA babies, and these higher levels were correlated with milder symptoms of allergy and lower SCORAD eczema scores. IL-10 was also significantly and negatively correlated with total IgE levels, indicating IL-10 plays a suppressive function against allergic inflammation. Such molecular mechanisms are supported in the directionality of results through KEGG pathway analysis: in the cytokine-cytokine receptor interaction pathway (hsa04060), IL-10 binds through the IL10R receptor, triggering downstream anti-inflammatory signaling; in the Jak-STAT signaling pathway (hsa04630), IL-10 activates STAT3, the latter triggering anti-immunostimulatory gene expression; in the T cell receptor signaling pathway (hsa04660), IL-10 activates regulatory T-cell production for preservation of immunological tolerance. Such molecular mechanisms are consistent with Legrand (2016), who highlighted IL-10's action in suppressing Th2 responses and crucial in maintaining Th1/Th2 balance towards prevention of hypersensitivity. In aggregate, these findings solidify IL-10 as a critical cytokine for protection against risk for allergy/immunity homeostasis during early life.

Although numerous studies on human milk proteomes and their potential to prevent allergy have reported promising findings, it is important to consider the confounding variables that could influence the findings of these studies. Donald *et al.* (2024) suggested that maternal age, mode of delivery, and early antibiotic exposure are confounding variables likely to influence the amount and quality of transferred secretory immunoglobulin A (SIgA) via breastfeeding. Jiang *et al.* (2021) accounted for geographical variables, maternal genetic characteristics, and secretor status and found that a strong association between Factor 2 proteome and reduced allergy risk was attenuated upon adjustment for geographical confounding variables. This suggests that the environment and lifestyle variables could be significant contributors. At the same time, Lupinek *et al.* (2019) suggested that exposure history of a mother, immune status, and breastfeeding exclusivity might determine the amount and specificity of transferred infant IgG, crucial to modulating

the infant's immune response. Finally, Manti *et al.* (2016) recognized that type of feeding, allergen exposure duration, and infant immunity variability could influence IL-10 production, which in turn influences the expression of allergic diseases in infants. These studies collectively underscore the need for future research to control for these variables to better isolate the effects of human milk proteomes in allergy prevention.

## CONCLUSION

In conclusion, this study highlights the role of human milk proteomes in preventing allergen sensitivity in infants. Seven proteomes were identified in this review which are secretory immunoglobulin A, IgG, vitronectin, CD81, Complement C4A, Immunoglobulin  $\gamma$ 4, and IL-10. The bioactive components in human milk contribute significantly in building the immune system through passive immunity, immunomodulation, and stimulation of gut health. These bioactive molecules inhibit allergic sensitization, protect against infections, invoke a synergistic immune response and thereby reduce the likelihood of developing allergic diseases like asthma, eczema, and allergic rhinitis. While the current evidence highlights the protective role of human milk proteomes in reducing allergy risk in infants, further research is needed to uncover the underlying mechanisms and long-term benefits. This includes methodologically robust studies that control for key variables such as maternal diet, genetics, and environment, while applying longitudinal designs and standardized protocols. A broader, multi-omics approach may also provide a more integrated understanding of how various milk components work together to promote immune tolerance. These efforts can ultimately inform targeted strategies for allergy prevention and early-life health promotion.

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