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BREAST MILK AS AN IMMUNOMODULATOR: SCIENTIFIC ADVANCES AND CLINICAL PERSPECTIVES IN NEONATAL HEALTH

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REVISÃO INTEGRATIVA DA LITERATURA

ABSTRACT

This study aimed to gather and analyze scientific evidence on the immunomodulatory role of breast milk, with emphasis on its bioactive components, protective effects, and clinical implications for neonatal health. It is an Integrative Literature Review, grounded in the principles of Evidence-Based Practice. The research question was structured according to the PICo strategy, considering newborns and infants as the population, the immunomodulatory and bioactive effects of breast milk as the phenomenon of interest, and neonatal health as the context. Searches were conducted between August and September 2025 in the PubMed, SciELO, ScienceDirect, and LILACS databases. Studies published between 2016 and 2025, in Portuguese and/or English, addressing the immunological components of human milk were included. Selection followed the PRISMA protocol and the Joanna Briggs Institute (JBI) levels of evidence. Fifteen studies met the inclusion criteria, demonstrating that breast milk functions as a dynamic immunological system capable of combining passive immunity - primarily mediated by secretory IgA - with active modulation of the infant's immune response through molecules such as lactoferrin, cytokines, and human milk oligosaccharides (HMOs). These elements exert antimicrobial, anti-inflammatory, and epigenetic actions, promoting intestinal microbiota balance and immune system maturation. Beyond its protective functions, human milk shows therapeutic potential, notably through the use of donor and pasteurized milk in cases of prematurity. It is concluded that breastfeeding is an effective, safe, and low-cost intervention to reduce neonatal morbidity and mortality and to strengthen long-term immunity.

Keywords: Human milk; Immunomodulation; Breastfeeding; Newborn; Human milk oligosaccharides.

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1- INTRODUCTION

Breast milk is widely recognized as the optimal source of nutrition for newborns, not only because it fulfills their nutritional needs but also because it plays an essential role in immune maturation and protection against infections. Its dynamic composition reflects a complex interaction between biological and environmental factors, which adapt to the specific demands of each stage of infant development. In addition to fundamental macronutrients and micronutrients, human milk contains a wide variety of bioactive components - such as immunoglobulins, cytokines, hormones, and immune cells - that confer anti-inflammatory, antimicrobial, and immunomodulatory properties (Ballard; Morrow, 2013; Young; McGuire, 2020).

The immunological importance of breast milk lies mainly in its ability to establish an immune bridge between mother and child, promoting the passive transfer of antibodies and stimulating both the innate and adaptive immune systems of the neonate. Secretory immunoglobulin A (sIgA), the main antibody present in human milk, acts as the first line of defense against respiratory and gastrointestinal pathogens, while proteins such as lactoferrin and lysozyme inhibit bacterial and viral growth. Meanwhile, human milk oligosaccharides (HMOs) modulate the intestinal microbiota and favor colonization by beneficial bacteria, playing a fundamental role in immunotolerance and in the prevention of allergic and inflammatory diseases (Verhasselt *et al*., 2024; Andreas *et al*., 2015).

Over the past decades, advances in immunology and molecular biology have expanded our understanding of the protective and therapeutic effects of breast milk. Recent studies demonstrate that its bioactive components not only prevent neonatal infections but also participate in the epigenetic regulation and long-term maturation of the immune system, with a potential impact on reducing the risk of autoimmune, metabolic, and cardiovascular diseases in adulthood (Victora *et al*., 2016; Surdacka *et al*., 2024). Such evidence reinforces the view of breastfeeding as a public health intervention with intergenerational effects that transcend immediate nutrition and involve complex and enduring immunoprotective mechanisms.

Given the clinical and epidemiological relevance of this topic, it becomes essential to gather and synthesize the latest scientific knowledge on the immunomodulatory

mechanisms of breast milk and their implications for clinical practice. Therefore, this study aims to compile and analyze scientific evidence on the immunomodulatory role of breast milk, emphasizing its bioactive components, protective effects, and clinical application perspectives in the context of neonatal and pediatric health.

2- METHOD

This study is an Integrative Literature Review (ILR), a methodological approach that allows for the identification, analysis, and synthesis of scientific knowledge produced on a given topic by integrating studies with different designs and methodological perspectives. Grounded in the principles of Evidence-Based Practice, this type of review seeks to systematically and critically combine empirical and theoretical research findings, facilitating the translation of scientific knowledge into clinical practice and contributing to the improvement of health care strategies (Lemes *et al*., 2021; Whittemore; Knafl, 2005). The review followed the stages proposed by Whittemore and Knafl (2005), complemented by the guidelines of Lemes *et al*. (2021), encompassing the identification of the research problem and objectives, establishment of eligibility criteria, design of search strategies, selection and critical appraisal of studies, categorization and synthesis of findings, and presentation of results.

The guiding question was structured according to the PICo strategy (Population, Phenomenon of Interest, and Context), which is considered suitable for qualitative and integrative reviews (Stern; Jordan; McArthur, 2014). The Population was defined as newborns and infants, the Phenomenon of Interest as the immunomodulatory and bioactive effects of breast milk, and the Context as neonatal health and the prevention of infectious and inflammatory conditions. Accordingly, the research question was formulated as follows: What scientific evidence is available in the literature regarding the immunomodulatory mechanisms of breast milk and their clinical implications for neonatal health?

The bibliographic search was conducted between August and September 2025 using controlled vocabularies from Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), as well as free terms related to the subject of study. Boolean operators AND and OR were applied in the following search expressions: (“Leite

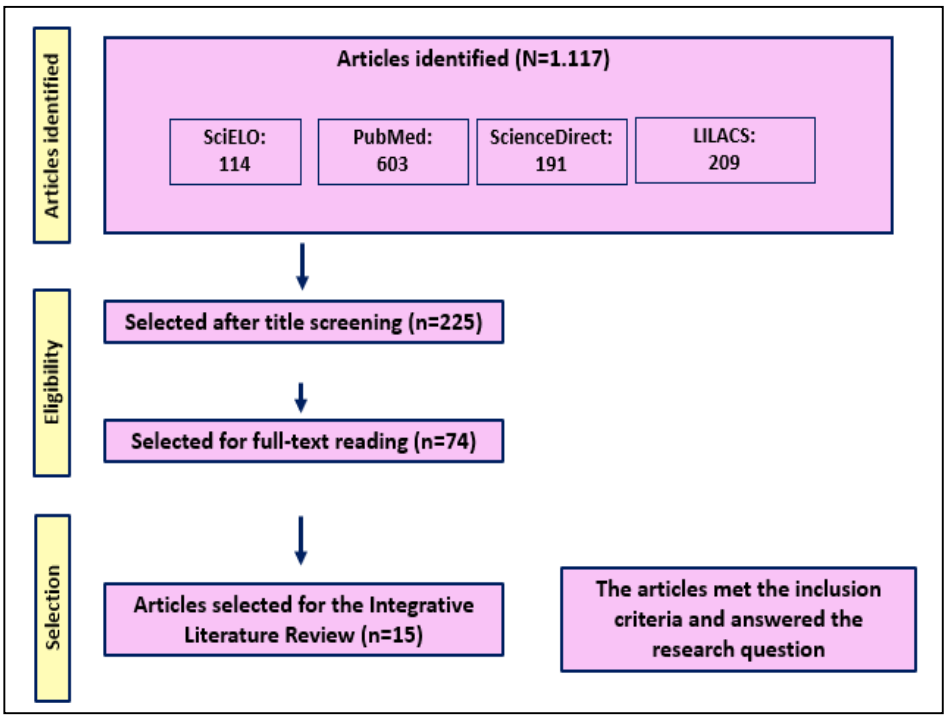
materno" OR "Breast milk") AND ("Imunidade" OR "Immunity") AND ("Recém-nascido" OR "Newborn"); ("Human milk" AND "Bioactive components"); and ("Breastfeeding" AND "Immune modulation"). Searches were performed in the PubMed, SciELO, ScienceDirect, and LILACS databases to include relevant technical and institutional documents addressing breastfeeding and neonatal immunology.

Inclusion criteria comprised original articles and review studies published between 2016 and 2025, available in full text and written in Portuguese, English, or Spanish, that discussed evidence regarding the bioactive components of human milk, their immunological effects, and clinical implications for neonatal and pediatric health. Exclusion criteria included duplicate papers, non-integrative reviews, dissertations, theses, letters to the editor, and publications not directly related to the topic.

The screening and selection process followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations, adapted to the integrative nature of this review (Moher *et al*., 2009). Initially, titles and abstracts were screened based on predefined eligibility criteria; subsequently, potentially relevant studies were read in full, and only those that met all inclusion parameters and aligned with the study objectives were selected. Data extraction and organization were conducted using a synthesis chart that included information such as first author, year of publication, journal, country of origin, study type, level of evidence, and main results related to the immunomodulatory mechanisms of breast milk.

The classification of evidence levels followed the methodological framework of the Joanna Briggs Institute (JBI) (Lockwood *et al*., 2020), which establishes the following hierarchy: Level I: meta-analyses and randomized controlled trials; Level II: experimental studies with control groups; Level III: quasi-experimental studies; Level IV: descriptive, observational, or qualitative investigations; Level V: case reports or case series; and Level VI: expert opinions, consensus statements, or technical reports. The process of identification, screening, and inclusion of studies is illustrated in the PRISMA Flow Diagram (Figure 1), which presents the stages of search and eligibility carried out throughout the review.

Figure 1: Flowchart of the Identification, Screening, Eligibility, and Inclusion of Studies According to the PRISMA 2009 Guidelines



Adapted from: Moher *et al.*, 2009

3- RESULTS

After applying the inclusion and exclusion criteria and conducting the screening process in accordance with the PRISMA protocol guidelines, fifteen scientific articles were selected to compose the corpus of this Integrative Literature Review. The analyzed studies encompassed diverse methodological approaches, including experimental, observational, and both integrative and systematic reviews addressing the immunomodulatory effects of breast milk.

The investigated contexts included research focusing on the bioactive components and immunocompetent cells present in human milk, studies on the passive transfer of antibodies and regulation of the intestinal microbiota, and investigations into the epigenetic and anti-inflammatory effects of breastfeeding on neonatal health and long-term immune development. Other works explored the correlation between breastfeeding and the reduced incidence of autoimmune, metabolic, and infectious diseases, as well as analyses of the therapeutic potential of specific components - such

as immunoglobulins, lactoferrin, cytokines, and human milk oligosaccharides (HMOs) - in immune protection and the maturation of the infant immune system (Carr *et al*., 2021; Albrecht; Arck, 2021; Verhasselt *et al*., 2024; Young; McGuire, 2020; Auer; Jarvs, Guttman, 2021).

The critical analysis of the findings allowed the organization of results into two analytical categories, which will be discussed in greater detail in the following section: (1) Immunomodulatory Mechanisms and Protective Effects of Breast Milk and (2) Clinical Implications and Therapeutic Perspectives in Neonatal Health. These categories reflect the multifactorial nature of the immunoprotection provided by breast milk, highlighting both the biological processes underlying its immune activity and its clinical application potential in contexts of prevention, intervention, and promotion of child health.

Table 1 below presents a synthesis of the studies included in the review, summarizing the title, first author, journal, year of publication, study type, level of evidence, and main findings related to the immunomodulatory mechanisms, clinical effects, and therapeutic perspectives of breast milk.

Table 1: Summary of studies included in the integrative review on the immunomodulatory, clinical, and therapeutic effects of human milk

Title	First Author (Year)	Journal	Study Type	Level of Evidence (JBI)	Main Findings
Antibodies in breast milk: pro-bodies designed for healthy newborn development	Verhasselt (2024)	Immunological Reviews	Systematic Review	I	Identified immunoglobulins, cytokines, and exosomes as key modulators of neonatal immune maturation and mucosal protection.
Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect	Victora (2016)	The Lancet	Cohort Review	II	Demonstrated long-term benefits of breastfeeding on immune, metabolic, and cognitive outcomes throughout life.
Role of human milk bioactives on infants' gut and immune health	Carr (2021)	Frontiers in Immunology	Systematic Review	I	Highlighted HMOs and cytokines as mediators of gut microbiota regulation and

					immune homeostasis in newborns.
Vertically transferred immunity in neonates: mothers, mechanisms and mediators	Albrecht (2021)	Frontiers in Immunology	Narrative Review	V	Described maternal antibody transfer and regulatory cytokines as major contributors to neonatal immune defense.
Immunologic components in human milk and allergic diseases with focus on food allergy	Burris (2021)	Seminars in Perinatology	Observational Review	IV	Correlated immune compounds in milk (IgA, TGF-β) with decreased risk of neonatal allergies and inflammatory responses.
Human milk composition: nutrients and bioactive factors	Ballard (2013)	Pediatric Clinics of North America	Descriptive Review	V	Described bioactive molecules, emphasizing lactoferrin, lysozyme, and HMOs as antimicrobial and immunoregulatory factors.
Immunologic properties of human milk and clinical implications in the neonatal population	Young (2020)	Neoreviews	Integrative Review	IV	Discussed passive and active immune mechanisms in breast milk supporting neonatal infection resistance.
Effect of maternal miRNAs and milk oligosaccharides on regulating the growth behavior of Bifidobacterium longum subsp. infantis	Yao (2025)	Journal of Functional Foods	Experimental Study	II	Demonstrated the synergistic action of HMOs and miRNAs in promoting probiotic growth and intestinal immunity.
Recent advances in the analysis of human milk oligosaccharides by liquid phase separation methods	Auer (2021)	Journal of Chromatography B	Analytical Study	III	Identified structural variations in HMOs linked to individual immune and metabolic profiles.
Epigenetic and immune mechanisms linking breastfeeding to lower breast	Surdacka (2024)	Medical Science Monitor	Systematic Review	I	Described epigenetic modulation and immune signaling pathways connecting

cancer rates					breastfeeding with reduced cancer risk.
Human milk as therapy: neurodevelopment and neonatal brain injury	Strobel (2025)	Seminars in Perinatology	Experimental Review	II	Demonstrated neuroprotective and anti-inflammatory properties of human milk in premature infants.
Clinical studies on the supplementation of manufactured human milk oligosaccharides: a systematic review	Schönknecht (2023)	Nutrients	Systematic Review	I	Evaluated synthetic HMOs as potential immunomodulators and prebiotic agents for neonatal therapy.
Human breast milk: a review on its composition and bioactivity	Andreas (2015)	Early Human Development	Narrative Review	V	Reviewed evidence on immune-active components of breast milk with implications for clinical application.
Unlocking the potential: a systematic literature review on the impact of donor human milk on infant health outcomes	Kashyap (2024)	Cureus	Systematic Review	I	Reported superiority of pasteurized donor milk over formula for immune protection and intestinal maturation.
DNA methylation mediates the association between breastfeeding and early-life growth trajectories	Briollais (2021)	Clinical Epigenetics	Experimental Study	II	Demonstrated that breastfeeding influences DNA methylation and epigenetic programming of immune and metabolic pathways.

Table 1: Summary of studies included in the integrative review on the immunomodulatory, clinical, and therapeutic effects of human milk.

4- DISCUSSION

The findings of this review confirm that breast milk transcends its nutritional function, constituting a complex biological system endowed with fundamental immunomodulatory properties essential for the healthy development of newborns. The literature demonstrates that its bioactive components act in an integrated manner on both innate and adaptive immunity, exerting broad antimicrobial, anti-inflammatory,

and epigenetic effects (Verhasselt *et al*., 2024; Victora *et al*., 2016). The synthesis of the analyzed studies reinforces that breastfeeding represents one of the most effective pillars of neonatal public health, significantly reducing infant morbidity and mortality while promoting long-lasting immunological benefits with effects extending into adulthood (Carr *et al*., 2021; Albrecht; Arck, 2021).

4.1 Immunomodulatory Mechanisms and Protective Effects of Breast Milk

The reviewed literature demonstrates that human milk contains a wide range of immunologically active molecules, including immunoglobulins, cytokines, lactoferrin, lysozyme, oligosaccharides, and maternal immune cells. These components act synergistically to defend the newborn, providing immediate passive immunity while simultaneously stimulating the maturation of the infant's own immune system (Burris *et al*., 2021; Ballard; Morrow, 2013; Young; McGuire, 2020). Secretory immunoglobulin A (sIgA) plays a central role by preventing pathogen adhesion to respiratory and intestinal mucosae, while lactoferrin inhibits bacterial growth through iron chelation and modulation of the inflammatory response.

Furthermore, human milk oligosaccharides (HMOs) represent one of the most promising fields in neonatal immunology. Recent studies indicate that these complex structures are not digested by the infant's body but act as prebiotic substrates that promote the selective growth of beneficial bacteria such as Bifidobacterium and Lactobacillus, which are essential for intestinal homeostasis and immune balance (Yao *et al*., 2025; Auer, Jarvas; Guttman, 2021). In parallel, breast milk contains microvesicles, exosomes, and microRNAs whose epigenetic actions influence the expression of genes related to immune response, oral tolerance, and the metabolic development of the neonate (Surdacka *et al*., 2024).

Another relevant aspect identified in the studies is the anti-inflammatory and protective effect of breast milk against respiratory and gastrointestinal infections, particularly in premature and immunologically immature newborns. The combination of maternal antibodies, regulatory cytokines (such as IL-10 and TGF-β), and growth factors grants human milk the capacity to modulate inflammatory responses and reduce the risk of necrotizing enterocolitis, neonatal sepsis, and other opportunistic infections

(Strobel *et al*., 2025; Albrecht; Arck, 2021; Carr *et al*., 2021). These findings reinforce the understanding that breastfeeding is a low-cost and highly effective intervention for promoting infant immunity, directly impacting hospitalization rates and strengthening collective health.

4.2 Clinical Implications and Therapeutic Perspectives in Neonatal Health

Scientific advances in understanding the immunological role of breast milk have driven new therapeutic perspectives that extend beyond natural nutrition. The clinical application of its bioactive components - such as recombinant lactoferrin, synthetic HMOs, and probiotics derived from human strains - has been explored in clinical trials aimed at preventing infections and modulating inflammatory responses in neonates admitted to intensive care units (Schönknecht *et al*., 2023; Carr *et al*., 2021; Andreas *et al*., 2015). These findings suggest the potential of biotechnologies inspired by human milk for use in infant formulas, immunotherapies, and strategies to prevent immune-mediated diseases.

In clinical settings, there is also growing recognition of donor and pasteurized human milk as a therapeutic resource in cases of extreme prematurity or when direct breastfeeding is not possible. Studies indicate that, although pasteurization reduces some enzymatic and cellular activity, processed human milk retains significant fractions of its immunological effects, proving superior to artificial formulas in terms of immune protection and intestinal development (Kashyap; Choudhari, 2024; Verhasselt *et al*., 2024; Young; McGuire, 2020). This finding reinforces the importance of human milk bank networks as essential public health policies for neonatal well-being.

Finally, the reviewed literature highlights the epigenetic and intergenerational dimensions of breastfeeding, showing that immunomodulatory mechanisms extend beyond the neonatal period and influence long-term metabolic and immunological programming (Briollais *et al*., 2021; Victora *et al*., 2016; Surdacka *et al*., 2024). Breastfeeding has been associated with a lower risk of autoimmune diseases, allergies, obesity, and even certain maternal and childhood cancers. In this sense, promoting, protecting, and supporting breastfeeding should not be understood merely as a nutritional recommendation but as a public health strategy capable of reshaping disease

trajectories and strengthening collective immunity from the earliest days of life.

5- FINAL CONSIDERATIONS

This study aimed to gather and analyze scientific evidence on the immunomodulatory role of breast milk, emphasizing its bioactive components, protective effects, and clinical application perspectives in neonatal and pediatric health. The synthesis of the fifteen included studies consistently demonstrates that human milk functions as a dynamic immunological system, combining passive immunity - primarily mediated by secretory IgA - with active modulation of the infant's immune response through antimicrobial proteins such as lactoferrin, regulatory cytokines, and human milk oligosaccharides (HMOs). Collectively, these elements provide anti-infective and anti-inflammatory benefits, regulate intestinal microbiota composition, and participate in epigenetic pathways related to immune maturation and long-term development.

From a clinical care perspective, the findings reinforce that promoting, protecting, and supporting breastfeeding remains one of the most cost-effective interventions in neonatal health, with the potential to reduce respiratory and gastrointestinal infections, hospitalizations, and early inflammatory conditions. In cases of prematurity or when direct breastfeeding is not possible, donor and pasteurized human milk emerge as superior alternatives to formulas, preserving a significant portion of immunological properties. These findings align directly with public health policies, the organization of human milk bank networks, and the ongoing need for multidisciplinary team training in breastfeeding counseling and clinical management.

From a technological and translational standpoint, promising opportunities are emerging, including the clinical evaluation of specific HMOs, the therapeutic use of lactoferrin, and probiotics designed to align with the infant gut ecosystem. Although the literature reports encouraging results, methodological heterogeneity across studies - regarding outcomes, follow-up duration, and population profiles - and the predominance of observational designs in part of the corpus limit the strength of recommendation for certain isolated interventions. Therefore, advancing rigorous clinical trials with standardized outcomes and stratification by prematurity, delivery mode, antibiotic exposure, and socioenvironmental context is strongly recommended.

Finally, there remains a relevant space for research integrating multi-omic approaches (metagenomics, metabolomics, and epigenomics) and assessing equity in access to breastfeeding practices and benefits, especially among vulnerable populations. Investigations into pasteurization processes and alternative processing techniques that minimize bioactive losses, as well as implementation studies that bridge evidence with routine practice in primary care and neonatal intensive care, could accelerate the real-world impact of discoveries. In summary, breastfeeding must be understood and operationalized as both an immunoprotective and public health strategy: by combining robust biological knowledge with structural policies and qualified clinical practices, a concrete pathway is established toward improved neonatal outcomes and healthier life-course trajectories.

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