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REVIEW ARTICLE

Role of maternal milk in providing a healthy intestinal microbiome for the preterm neonate

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The immature gastrointestinal tract of preterm neonates leads to a delayed and distinctive establishment of the gut microbiome, making them susceptible to potentially pathogenic bacteria and increasing the risk of infections. Maternal milk, recognized as the optimal source of nutrition, plays a multifaceted role in modulating the gut microbiome of premature newborns. Human milk oligosaccharides, acting as prebiotics, provide essential nourishment for key bacteria such as *Bifidobacterium*, contributing to the proliferation of beneficial bacterial populations. Additionally, maternal milk is rich in Immunoglobulins that stimulate immune cell responses, providing protective effects on the infant's gut mucosa. Moreover, bioactive proteins such as secretory immunoglobulin A (SIgA), lactoferrin, lysozyme, and mucins play a crucial role in defending against pathogens and regulating the immune system at the cellular level. These proteins contribute not only to infection prevention but also emphasize the impact of breast milk in fortifying the body's innate defenses. This multifaceted role of maternal milk, including essential nutrients, beneficial bacteria, and bioactive proteins, highlights the importance of promoting the mother's own milk feeding in the Neonatal Intensive Care Unit (NICU). It not only optimizes the long-term outcomes and well-being of preterm infants but also provides a holistic approach to their health and development.

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IMPACT:

- This article contributes to the current understanding of the relationship between breastfeeding and the intestinal microbiota.
- Fill gaps in existing literature about the subject.
- Provides new insights for future research.

INTRODUCTION

Full-term newborns and preterm infants differ in their gut microbiome composition. While term infants possess a diverse amount of beneficial bacteria that contribute to immune system fortification and infection prevention, preterm infants exhibit reduced microbial diversity and an increased presence of pathogenic bacteria.[1] Maternal milk, as the primary source of nutrition for humans and other mammalian species, plays a crucial role in infant development. Through breastfeeding, infants receive probiotics, such as *Bifidobacterium* and *Lactobacillus*, which can shape and modulate the infant's microbiota.[2] In contrast to term infants, preterm newborns have less stable gut microbiomes and lower bacterial diversity, which may increase their vulnerability to infections and other complications.[3] Moreover, preterm neonates possess underdeveloped immunity and intestinal barriers, further predisposing them to bacterial infection.[4]

Mother's own milk (MOM) plays a critical role in the establishment of the neonatal intestinal microbiota. Besides probiotics, it contains various substances, including growth factors and immunomodulatory molecules, that interact and help regulate the neonatal immune system. These components also contribute to antimicrobial activity and provide anti-inflammatory benefits.[5] The relationship between the neonatal microbiome and maternal milk involves the transfer of bacteria, bacteriophages, viruses, and immunoglobulins from the mother to the infant.[6,7] Moreover, MOM significantly contributes to the prevention of Late-onset sepsis (LOS) and Necrotizing Enterocolitis (NEC), which are major diseases and leading causes of mortality in the Neonatal Intensive Care Unit (NICU). The utilization of MOM has played a decisive role in reducing the incidence of these diseases.[8,9] This review aims to explore the scientific literature on the influence of maternal milk on the gut microbiome of premature neonates.

PRETERM NEONATE MICROBIOME COMPARED TO TERM INFANTS

The colonization of gut bacteria plays a critical role in neonate hosts, with particular importance in preterm infants.[10] The timing of birth (prematurity versus term newborns) and hospitalization contribute to the development of distinct microbiomes in these infants.[11]

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Factors negatively impacting the intestinal microbiome of preterm infants

Timing of birth. Many factors negatively affect the intestinal microbiome of preterm babies, one of them is the time of birth. Compared to term infants, preterm neonates experience a delayed establishment of the intestinal microbiome due to their immature gastrointestinal tract, including decreased defense cells, compromised barrier function, and altered mucosa.[12] This immaturity also extends to their immune system, making them more susceptible to infections. Due to lower levels of immune cells, their immune response is decreased. Also, they do not fully recover their immune function by the seventh day after birth. This delayed recovery means their immune system remains weakened during this critical early period of life, resulting in slower responses to infections compared to full-term infants.[13]

Hospitalization. Another factor that harms the gut microbiome of preterm infants is the hospitalization. Preterm babies experience extended hospital stays compared to term infants, making them more exposed to opportunistic pathogen bacteria that may colonize the gut. For example, a prospective study conducted at Tampa General Hospital, University of South Florida, identified a predominant variant of *Klebsiella* in the gut of almost all premature neonates. It suggests a potential common source, possibly originating from the hospital environment. Besides, the research showed that this *Klebsiella* variant increased from being present in 44% of preterm infants admitted to the NICU in the 1st and 2nd weeks, to 78% in the 4th week of hospitalization (range of 0–99%).[14] It is worth emphasizing the significance of *Klebsiella* as a Gram-negative opportunistic pathogen, particularly in individuals with compromised immune systems. This bacterium is highly prevalent in healthcare settings and is recognized as a major cause of nosocomial infections.[15]

Mode of delivery. The mode of delivery also creates different microbiomes comparing preterm to term infants. For healthy-term infants, what predominates is vaginal deliveries.[16] However, cesarean section (CS) is commonly chosen as the mode of delivery for preterm infants to reduce the risks associated with vaginal birth.[17] In this meaning, a study highlights the importance of the mother's gut for the vaginal delivery of newborns in the early colonization of their gut microbiota by beneficial bacteria, especially *Bifidobacterium*.[18] Unfortunately, CS, the preterm main mode of delivery, is linked with reduced beneficial bacteria (such as *Bifidobacterium*) and higher colonization by pathobionts (such as *Clostridium*) at 3 months.[19]

Antibiotics. Another element negatively affecting the gut microbiome of preterm infants is the use of antibiotics. Research indicates that drugs such as meropenem, cefotaxime, and ticarcillin–clavulanate significantly reduce the diversity of gut bacterial species in these infants. This reduction disrupts the balance of bacterial populations, leading to dysbiosis. Moreover, antibiotics promote the development of antibiotic-resistant genes and multidrug-resistant bacteria from genera like *Escherichia*, *Klebsiella*, and *Enterobacter*, which are known for causing infections.[20] Not only infants' use of antibiotics is harmful to their microbiome, but also intrapartum use by mothers. Although further research is needed to explore the health consequences of these associations, intrapartum antibiotics, regardless of delivery mode, are associated with infant gut microbiota dysbiosis, and breastfeeding modifies some of these effects.[21]

Distinctive bacterial colonization

Preterm infants commonly experience delayed colonization, particularly in the case of *Bifidobacterium*, which can be attributed to their gestational age.[22] *Bifidobacteriaceae* is a prevalent bacterial group in infants' healthy gastrointestinal tract[23,24] that contributes significantly to the overall microbiome abundance and plays a vital role in maintaining gastrointestinal homeostasis.[25] However, preterm infants often exhibit a high prevalence of potentially pathogenic bacteria, including *Staphylococcus*, *Enterobacteriaceae* (specifically the genera *Klebsiella* and *Escherichia*), *Enterococcaceae*, as well as other genera such as *Lactobacillus* and *Weissella*.[26–28] Notably, *Staphylococcus* has been associated with systemic inflammation in preterm infants, leading to an increased risk of adverse outcomes and prolonged hospital stay.[29] *Enterobacteriaceae* have been linked to Carbapenem-resistant infections and are frequently detected in newborns with sepsis.[30,31]

Another study conducted in the Neonatal Intensive Care Unit (NICU) revealed that the gut microbiota of preterm neonates is characterized by a limited number of bacterial families, including *Bifidobacteriaceae* (30.5%), *Enterobacteriaceae* (21.2%), *Staphylococcaceae* (15.1%), *Enterococcaceae* (12.2%), *Streptococcaceae* (10.7%), and *Clostridiaceae* (3.2%). These bacterial families collectively constitute the majority of the identified families, representing 92.4% of the total.[32] The presence of these bacteria significantly impacts neonatal development, with *Staphylococcaceae*, *Streptococcaceae*, and *Clostridiaceae* being implicated in cases of Late-onset sepsis (LOS), while *Clostridiaceae* and *Enterococcaceae* are associated with Necrotizing Enterocolitis (NEC).[33,34]

The microbiome diversity in preterm neonates is generally compromised, exhibiting limited bacterial patterns and an increased prevalence of potentially pathogenic bacteria[35] (Fig. 1). However, the composition of the microbiome can be modulated by maternal milk, as infants who are fed with MOM tend to have a more favorable initial bacterial diversity and gradual acquisition of microbiome diversity compared to those who are formula-fed.[36,37]

IMPORTANCE OF MOM TO THE INTESTINAL MICROBIOTA AND IMMUNITY

The World Health Organization recommends exclusive breastfeeding starting from the first hour after birth and continuing for up to 6 months.[38] Maternal milk is widely acknowledged as the optimal source of nutrition for both preterm and term infants during early life.[39] Besides providing complete nutrition, it plays a critical role in reducing inflammation and providing antibodies.[40,41] It is now recognized that contrary to the belief held 20 years ago, breast milk is not sterile. It harbors a diversity of microorganisms that actively contribute to shaping the newborn gut microbiota. A cohort study identified more than 35 different bacterial genera within the first 30 days after birth. The most prevalent genus was *Streptococcus*, followed by *Bifidobacterium*.[42]

Protective benefits of maternal milk components

In contrast to formula feeding, MOM feeding is associated with lower rates of morbidity and mortality related to immune-related diseases, especially in the NICU[43] (Fig. 2). It offers protection to vulnerable infants during the early stages of life[44] and contains bioactive components that promote immune health. Besides, maternal milk is rich in oligosaccharides, which are complex carbohydrates that are not digested by the neonate but instead fermented by beneficial intestinal bacteria.[45,46] These oligosaccharides exhibit prebiotic effects[47,48] and are essential for shaping the gut microbiome by promoting the growth of beneficial bacteria (Fig. 3),[49,50] including *Bifidobacterium*,[51] considered the most essential probiotic group[52] and *Lactobacillus*.

Proteins and lipids. Other components of maternal milk, including proteins and lipids, can also benefit the gut microbiome of premature infants. For example, MOM contains immunoglobulins and immunological factors that are crucial for preventing infections (Fig. 3).[53,54] In this meaning, the lipids

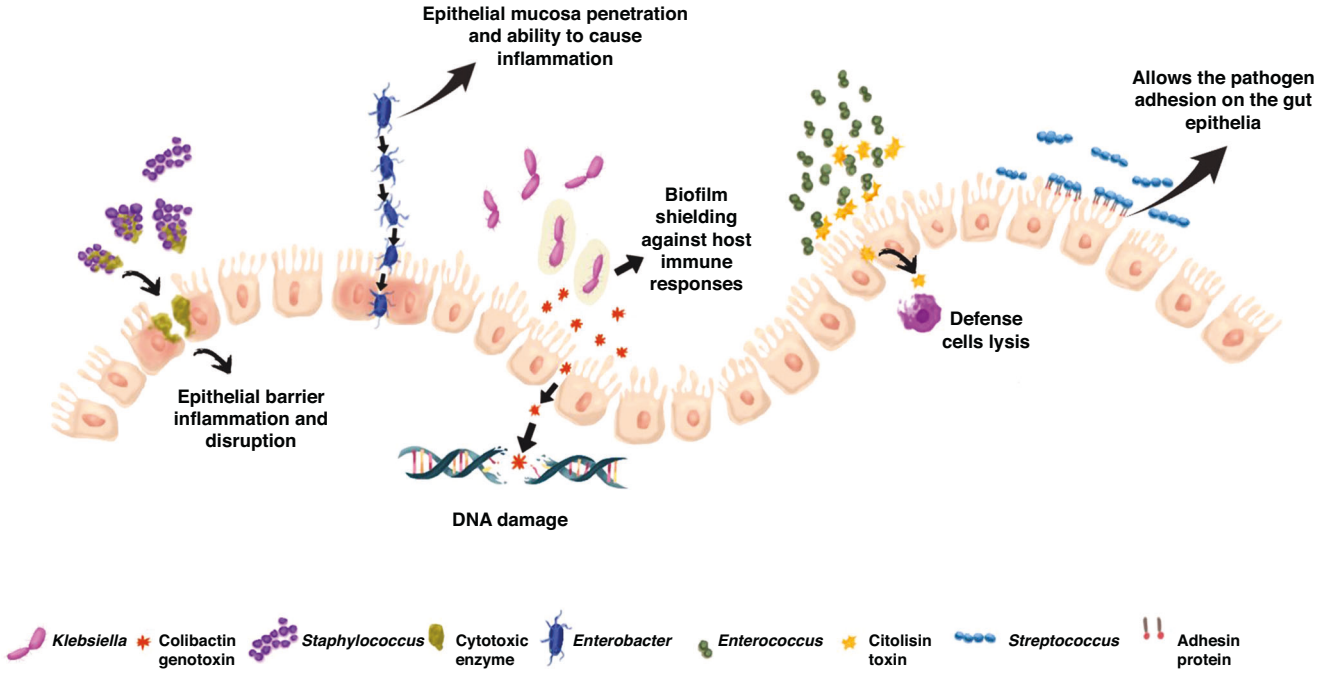

Fig. 1 Admission to the Neonatal Intensive Care Unit might affect the preterm neonate gut microbiome by being a source of potentially pathogenic bacteria. The illustration represents these bacteria families, their virulence factors, and how they may damage the intestine epithelia. *Staphylococcus* can generate cytotoxic enzymes that lead to inflammation and the disturbance of the gut epithelial tissue. *Enterobacter* is highlighted for its capability to infiltrate mucosal tissues, resulting in the induction of inflammation. *Klebsiella* is well-known for its skill in generating biofilms, which act as a defensive barrier against the host's immune responses. Additionally, it produces a genotoxin known as Colibactin, responsible for inducing DNA damage. *Enterococcus* produces citolisin toxins that leads to the lysis of immune cells. Besides, *Streptococcus* harbors an adhesion protein that facilitates the pathogen's attachment to the gut's epithelia.

and protein (mucin) are both essential constituents of neonatal gut mucus.[55] The primary function of the intestinal mucus layer is to safeguard the intestines from mechanical, chemical, and biological hazards. It aids in maintaining intestinal balance by establishing a protective layer that envelops the intestinal cells. This layer acts as a shield, safeguarding the cells from contact with external elements, toxic substances, digestive enzymes, and bacteria.[56]

Enhancing the increase of alpha diversity

Besides, the intestinal microbiota of preterm neonates is highly vulnerable and can be disrupted by various factors, such as the administration of antibiotics and exposure to harmful bacteria. Mother's milk plays a crucial role in supporting the metabolic function of energy and nutrient utilization in premature infants and is indispensable for promoting an increase in alpha diversity, which refers to the richness of microbial species within an individual's gut microbiome.[7]

MOM supporting the preterms' immune system

Studies have demonstrated that mothers who delivered preterm infants had notably higher levels of Immunoglobulin A (IgA) in their colostrum compared to those who delivered term neonates. One believes that this intense concentration of IgA is an adaptive response aimed at protecting the delicate gut mucosa of preterm infants.[57] IgA, present in MOM, is essential for establishing a healthy gut microbiome.[58] Neonates with a deficiency in this immunoglobulin exhibit an increased abundance of *Enterobacteriaceae*.[59]

All these advantages of MOM feeding contribute to the development of a thriving gut microbiome, which exerts lifelong impacts on the neonate. It stimulates and regulates responses of gut tissues and immune cells,[60,61] while also fulfilling metabolic, protective, and trophic functions.[62]

MICROBIOME DIFFERENCES BETWEEN PRETERM INFANTS FED WITH MOTHER'S MILK AND THOSE FED WITH FORMULA

The proper development of the intestinal immune system is essential for the initial colonization of beneficial bacteria in preterm infants. MOM plays a significant role in facilitating the transfer of bacteria from mother to infant, thereby promoting the establishment of a diverse and protective microbiome in preterm neonates.[63]

Bacterial diversity

Research conducted at the Neonatal Intensive Care Units (NICUs) of Peking the Third Hospital and People's Hospital of Nanpi Country demonstrated that preterm infants who received MOM had a higher gut microbiota diversity compared to those fed with formula. The study also found that the alpha diversity of the gut microbiota, which represents the richness of microbial species, tended to be higher in infants receiving mother's milk compared to those who did not.[64] Similarly, a study conducted at the Neonatology Section of Hospital de Clínicas de Porto Alegre, Brazil, reported similar findings, with exclusively MOM-fed preterm infants showing greater microbiome richness (average of 85 Operational Taxonomic Units) compared to infants fed with different methods (average of 25 Operational Taxonomic Units).[65] These studies highlight the positive impact of MOM on the diversity and composition of the gut microbiota in preterm infants.

Bacterial genera

A prospective study revealed that preterm neonates fed with MOM had a higher abundance of *Lactobacillales* and *Bacillales* (bacterial families associated with a healthy gut microbiome) compared to formula-fed infants, who exhibited a greater amount of *Enterobacteriales* (potentially pathogenic bacterial families).[66]

Furthermore, a study conducted in a Lebanese hospital unveiled the significant influence of feeding type on the intestinal microbiota of preterm neonates. A comparison between breast-feeding and formula-feeding revealed disparities in colonization after two and three weeks of life, with mother's milk-fed infants exhibiting favorable colonization by *Bifidobacterium* and *Lactobacillus*.[67]

It is noteworthy that *Lactobacillus* demonstrates substantial probiotic potential,[68] and the prevalence of bifidobacteria in the gut microbiota is linked to a reduction in the colonization of bacteria carrying antimicrobial resistance genes. This correlation implies that bifidobacteria play a crucial role in combating infections.[23] On the contrary, exclusively formula-fed infants tend to possess a microbiota characterized by elevated levels of *Escherichia coli* and *Clostridia*.[68] *Escherichia coli* is a potentially pathogenic bacterium renowned for its enterotoxic properties and its role in gastrointestinal infections.[69]

Fig. 2 A representation of how the preterm neonates are fed with maternal milk in the Neonatal Intensive Care Unit. When feasible, the primary choice is to provide premature infants with their mother's expressed breast milk, acquired through pumping and recognized as the best source of nutrition. In cases where mother's milk production is insufficient or unavailable, pasteurized donor human milk from a milk bank may be utilized. This donor milk undergoes a pasteurization process to ensure safety and nutritional quality. When it comes time to feed the preterm baby, the nurse begins by providing the mother's milk prepared for feeding. This may involve warming it to an appropriate temperature and verifying its freshness and cleanliness. Following these preparations, the preterm infant is nourished using a flexible feeding tube, such as a nasogastric tube.

MOTHER'S MILK BENEFITS IN PREVENTING INFECTIONS

Understanding important infecctions

NEC and LOS are the highest causes of morbidity and mortality in Neonatal Intensive Care Units (NICU),[70,71] which is why they are important diseases addressed in this article. It is worth noting that most cases of NEC and LOS occur in preterm infants,[72,73] resulting in tissue injury and intestinal barrier integrity loss.[74] NEC affects more than 4000 premature neonates yearly and has a mortality rate of nearly 33%[75]; LOS affects 20 to 38% of very preterm infants in the first 120 days of life and has a mortality rate of 13–19%.[8] Survivors of these conditions may also experience long-term morbidity, including neurodevelopmental delays.

Necrotizing enterocolitis (NEC) is a complex gastrointestinal disorder marked by inflammation and necrosis of the intestinal tissue. It encompasses a variety of factors, including intestinal immaturity, alterations in the gut microbiota, and compromised immune response, contributing to its development.[76] Late-onset neonatal sepsis (LOS) is a term used to describe sepsis that develops in newborns, particularly preterm infants, after the first three days of life.[77]

Molecular mechanisms of NEC. In the meaning of discovering the molecular mechanisms underlying the onset of Necrotizing Enterocolitis (NEC), researchers have highlighted the pivotal role played by the receptor for lipopolysaccharide derived from Gram-negative bacteria in its pathogenesis. This receptor, known as Toll-like Receptor 4 (TLR4), is predominantly present in immune system cells, particularly leukocytes. TLR4 specifically recognizes components unique to Gram-negative bacteria, such as lipopolysaccharide (LPS). After identifying these bacterial elements, TLR4 initiates an immune response by activating the pro-inflammatory

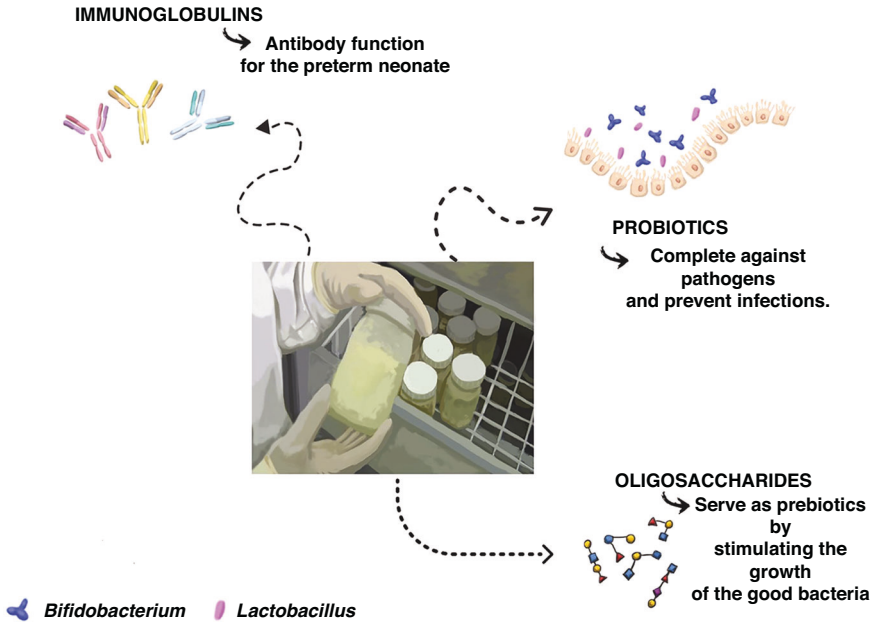

Fig. 3 Maternal milk is essential not only to provide complete nutrition to the premature. The illustration represents important substances such as immunoglobulins, probiotics, and oligosaccharides that are found in human milk to improve the health condition of the preterm neonate. The accompanying illustration depicts essential elements present in human milk that play a pivotal role in enhancing the health of premature babies.

transcription factor NFκB, serving as a key player in eliminating invading pathogens. Studies suggest that TLR4 signaling significantly contributes to the observed pathological consequences in NEC, implying its potential crucial role in NEC pathogenesis, although further research is needed.[78]

Dysbiosis influencing NEC and LOS. Moreover, one cause of NEC and LOS is dysbiosis,[72] which is characterized by an altered or disrupted state of the gut microbiota, where there is an unbalance in the diversity and abundance of microorganisms residing in the gastrointestinal tract. Besides, it is known that the preterm gut microbiota is marked by a restricted range of bacterial families. Also, is said that these diseases are the most general consequences of dysbiosis[73]; an abnormal microbiota may compromise the intestinal barrier integrity, which results in inflammation and the translocation of potentially pathogenic bacteria to the bloodstream, causing LOS.[79] Research showed that *Clostridia*, more often *C. neonatale* and *C. butyricum*, is notably more found in cases of NEC,[80] while *Staphylococcus* is more related to cases of LOS[81]; both found in preterm infants' gut microbiomes.

Mother's milk role in NEC and LOS

Despite the severity and significance of these diseases, MOM has the potential to impact their occurrence. Exclusive mother's own milk feeding during the initial 14 days of life has been linked to reduced chances of developing NEC and increased survival rates.[82] Additionally, the failure of early enteral feeding with MOM has been associated with LOS,[83] if early maternal milk feeding was successful, it is expected that the rates of LOS would decrease.

The preterm neonate gut has an overgrowth of the Proteobacteria phylum,[84] which englobes families such as *Escherichia*, these families are considered potentially pathogenic bacteria and are related to the development of NEC; whereas Firmicutes and Bacteroidetes are decreased in preterm infants, they are considered important primary consumers of maternal milk oligosaccharides, involved in breaking down complex carbohydrates and fiber, directly influencing nutrient absorption and associated with a health microbiome.[85–87]

As previously stated, maternal milk oligosaccharides (HMOs) serve as prebiotics and have the potential to impact NEC and LOS by improving the immune system and the quality and diversity of the gut microbiota. Research indicates that HMOs are a potential therapy to prevent NEC.[88] Another study has revealed that HMOs selectively promote the growth and activity of beneficial bacteria in the gut, such as Bifidobacteria, which are crucial for intestinal health and immune function. It is widely recognized that specific HMOs possess antiadhesive properties, which play a significant biological role attributed to HMOs. By impeding the attachment of bacteria to the surfaces of epithelial cells, HMOs have the potential to inhibit the colonization and growth of pathogens in the mucosal surfaces of the gut. Recent studies have also shown that the presence of HMOs inhibits the proliferation of *Streptococcus agalactiae*, a strain associated with Group B *Streptococcus*, known for its occasional infection-causing capabilities.[50]

Based on these findings, is important to relate that MOM-fed preterm neonates have a lower incidence of NEC compared to formula-fed ones.[89] It can be assumed that an optimistic NEC prevention is MOM feeding,[90] and the initiation of maternal milk use is also associated with a lower risk of developing LOS.[80]

INTERACTIONS OF BIOACTIVE PROTEINS IN MOM AGAINST PATHOGENS

Understanding the intricate relationship between bioactive proteins in MOM at the cellular level and their effects on harmful organisms is crucial for grasping the establishment of a robust immune response in breastfed infants. These proteins extend beyond nutritional functions, they contribute to the defense against pathogens and the regulation of the immune system. Proteins like immunoglobulins, mucins, lactoferrin, lysozyme, haptocorrin, and casein interactions can repel potential threats.[91] These interactions not only contribute to infection prevention but also emphasize the considerable impact of breast milk in fortifying the body's innate defenses at a cellular level.

Secretory immunoglobulin A

Secretory immunoglobulin A (SIgA), a highly abundant protein in mother's milk, is now recognized for its crucial role in regulating microbial colonization and influencing immune responses in infants. SIgA effectively performs its conventional antibody role by neutralizing and eliminating pathogens. This elimination process involves agglutination, wherein SIgA induces the clumping of bacteria. Particularly in the case of rapidly multiplying bacterial cells, this clumping aids the movement of bacteria through and out of the intestine. Furthermore, SIgA serves a preventive function in impeding the translocation of pathogenic bacteria across the epithelium. The binding to SIgA can downregulate genes linked to virulence, fostering a harmonious relationship between the host and microbes in the gut. Remarkably, SIgA facilitates the establishment of symbionts in the gut by promoting microbial adherence to the epithelium and biofilm formation. The varied glycan structures on SIgA, differing among individuals, also act as a carbon source for beneficial bacterial growth.[92]

Mucin, lactoferrin, lysozyme, haptocorrin, and k-casein

A study has underscored the crucial involvement of other bioactive proteins in MOM for premature infants. Mucins, specifically coating milk fat globules, form a chemical barrier referred to as milk fat globule membrane proteins. Despite representing only about 1–2% of all maternal milk proteins, they intricately contribute to shaping the composition of milk, which contains many captivating components. Unfortunately, existing infant formulas do not integrate these mother's milk fat globule membrane proteins. Lactoferrin and lysozyme collaborate synergistically to protect against pathogens. Initially, lactoferrin tightly binds to components of the outer cell membrane, such as lipopolysaccharides in Gram-negative bacteria, creating openings in the membrane. Subsequently, lysozyme penetrates the glycomatrix of the bacteria, breaking it down and effectively eliminating the pathogen. Additionally, the iron-free form of lactoferrin, the predominant form in breast milk, can combat pathogens like *Streptococcus* and *Escherichia coli* and inhibit the growth of *Helicobacter pylori*. Not only lactoferrin but also haptocorrin, even in very low concentrations, has proven effective against *Escherichia coli*. Furthermore, k-casein in MOM is heavily glycosylated (approximately 40%) and acts as an inhibitor of bacterial adhesion, capable of impeding the attachment of *Helicobacter pylori* to human gastric mucosa. This study intriguingly affirms the collaborative effectiveness of bioactive proteins in breast milk against pathogens.[91]

INTERACTIONS OF HUMAN MILK OLIGOSACCHARIDES (HMOS) AGAINST PATHOGENS AND THEIR IMPORTANCE TO THE MICROBIOME

HMOs as prebiotics

HMOs are the third most abundant component of human milk.[93] HMOs are crucial in shaping the neonate's gut microbiota by acting as prebiotics for protective bacteria, especially *Bifidobacterium*.[51] A cohort study stated that bifidobacteria are the main consumers of HMOs.[24] These bacteria species have specialized mechanisms to efficiently import, break down, and utilize HMOs as a carbon source.[94] Besides, research highlights that *Bifidobacterium* strains in early preterm infants exhibit unique genetic capabilities for HMO metabolism, allowing for the breakdown of diverse oligosaccharides and host-derived glycoproteins,

contributing to postnatal intestinal barrier maturation.[95] Furthermore, HMO-utilizing bifidobacteria have been associated with improved intestinal barrier integrity and reduced inflammatory responses, emphasizing their role in barrier maturation and their potential to decrease intestinal permeability.[96]

HMOs in immune responses

Oligosaccharides play an important role in immune responses, specifically in leukocyte extravasation and adhesion. Certain HMOs attach to proteins in these cells, modulating their migration toward inflamed tissues to prevent excessive infiltration, which can lead to tissue damage. This modulation potentially explains why infants fed mother's milk experience fewer inflammatory diseases.[97]

HMOs against pathogens

HMOs have been found to disrupt the early interactions between *Candida albicans* (the main cause of fungus diseases in NICU)[98] and premature gut epithelial cells by delaying the fungus's transformation into its invasive hyphal form. This delay impairs the fungus's ability to make stable contacts and invade host cells, which could help protect infants from fungal infections.[99] In addition, HMOs have antibiofilm properties and can inhibit the growth of potentially pathogenic bacteria, especially like group B *Streptococcus*,[100,101] contributing to the maintenance of a healthy intestinal microbiota.

Explanation for the HMOs' pathogenicity modifications

Certain oligosaccharides function as soluble receptor analogs, acting as decoys in the intestinal lumen. They either bind to proteins or exist in a free form, misleading bacteria into attaching to them instead of the oligosaccharides attached to the brush-border membrane of the small intestinal mucosa. According to the review, this phenomenon has been confirmed in multiple studies conducted in different countries.[91]

CONCLUSIONS

In conclusion, the multifaceted benefits of maternal milk for preterm neonates extend far beyond its nutritional value. Through the provision of essential nutrients, probiotics, bioactive proteins, and oligosaccharides, mother's milk actively shapes the gut microbiome, improves the immune system, and acts as a powerful defense against infections. The reduction in the incidence of diseases such as Late-onset sepsis (LOS) and Necrotizing Enterocolitis (NEC) underscores the critical role of MOM feeding in the Neonatal Intensive Care Unit (NICU). The positive impact of maternal milk on the gut microbiome diversity and composition, particularly in comparison to formula feeding, emphasizes the significance of this natural resource in promoting the overall health and development of preterm infants. Encouraging and supporting mother's milk feeding practices in the NICU can lead to long-term health benefits, illustrating the enduring influence of maternal milk on preterm neonates' well-being.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available through Google Scholar and Pubmed repositories. The articles related to these datasets can be accessed via the following platforms: https://pubmed.ncbi.nlm.nih.gov/ and https://scholar.google.com/.

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Ana Catarina de Castro Natal designed the structure of the article, conducted the literature review, analyzed it, and wrote the manuscript. Ralciane de Paula Menezes assisted in the writing of the article, and Denise Von Dolinger de Brito Röder guided the writing process and proofread the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT TO PARTICIPATE

Patient consent was not required as this study is a review and did not involve the collection of patient data.

ADDITIONAL INFORMATION

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