

Review

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Review

The Benefits of Human Breast Milk in Neonates and Infants

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Abstract

Human breast milk evolves beyond simple nutrition to function as a complex signaling system that promotes neonatal development. This review analyzes the bioactive components, delineating how its specific constituents compensate for the physiological vulnerabilities of the neonate. Additionally, the distinct roles of colostrum and mature milk are in fortifying the immature immune system and promoting gastrointestinal maturation. Focus is placed on the prevention of necrotizing enterocolitis, where milk oligo-saccharides and microbiome function to maintain mucosal integrity and symbiosis, while preventing pathogens' adhesion. Furthermore, it is evaluated how breastfeeding duration is linked to long-term metabolic and immunological programming. Mi-croRNAs and bioactive lipids actively modulate gene expression and immune responses, thereby reducing the incidence of metabolic diseases and childhood malignancies. By integrating findings, this article underscores the irreplaceable role of breast milk in clinical dietetics and pediatric care.

Keywords: breast milk; neonate; bioactive factors; immune system

1. Introduction

Human breast milk is universally recognized by international health authorities, including the World Health Organization (WHO) and the American Academy of Pediatrics (AAP), as the biological gold standard for infant nutrition [1,2]. It is a specific complex biological fluid that has evolved not merely to provide energy for growth, but to function in supporting the physiological development. It is valued for its macronutrient content, balancing proteins, lipids, and carbohydrates to match the infant's metabolic rates and for its bioactive capacity, containing thousands of non-nutritive factors that are critical for neonatal survival and long-term health programming [3,4].

The complexity of the breast milk is immediately evident in the initial phase of lactation. Colostrum, the first fluid secreted, is characterized by its unique composition and high concentration of immunological factors, such as secretory Immunoglobulin A (sIgA), lactoferrin, and various growth factors, prioritizing early immunological defense and gut maturation [5–7]. Over the first month of life, the transitioned mature milk, high in lactose and lipids, is balanced to meet the energy demands of the rapidly growing infant [3].

At birth, the immune system is significantly underdeveloped, characterized by limited production of immunoglobulins and B lymphocytes, delayed neutrophil activity, and a restricted cell-mediated immune response [8]. Human milk actively bridges this gap by transferring approximately 10^8 maternal leukocytes daily, along with crucial antimicrobial proteins, such as lysozyme and lactoferrin, which work synergistically against bacterial pathogens [9–12].

Furthermore, maternal antibodies support the adaptive immunity, with sIgA facilitating antigen recognition and uptake by intestinal dendritic cells [13,14].

The protective effect of the breast milk is very pronounced in mitigating life-threatening acute morbidities, particularly necrotizing enterocolitis (NEC) in preterm infants [15]. Human breast milk counteracts this through factors like human milk oligosaccharides (HMOs), which help modulate the gut microbiota, and heparin-binding EGF (HB-EGF), which is critical for repair and maturation of the enteric nervous system and intestinal mucosa [16–18]. Beyond its immune-boosting effect, breast milk plays a primary role as a probiotic, delivering bacterial species and influencing the gut microbiome [19,20].

The benefits extend beyond the lactation period, influencing health outcomes into the rest of the life. Epidemiological data indicate a dose-dependent relationship between breastfeeding duration and protection against chronic non-communicable diseases. This includes a reduced risk of metabolic syndrome and type 2 diabetes [21–23]. Additionally, immunomodulatory properties are linked with decreased risk of atopy and asthma, and specific childhood cancers like leukemia [24–26].

This review aims to provide a comprehensive analysis of the bioactive composition of human milk, examining how its immunologic, trophic and microbiome-modulating components interact to protect against acute neonatal morbidity and program long-term health resilience.

2. Breast Milk Composition

Colostrum is the initial fluid that is secreted immediately after birth, characterized by its unique volume, appearance, and composition. During the first few postpartum days, it is produced in low quantities and contains immunologic components, including secretory IgA, lactoferrin, leukocytes, and crucial developmental factors such as epidermal growth factor [5–7]. In addition, its low content of lactose indicates a primary immunologic and trophic rather than nutritional function. Furthermore, the mineral profile of colostrum differs significantly from mature milk, presenting elevated levels of sodium, chloride, and magnesium, and decreased concentrations of potassium and calcium [6,7]. Following the initial colostrum stage, transitional milk is produced, typically spanning from five days up to two weeks postpartum. This phase marks a significant increase in milk production to meet the evolving nutritional and developmental demands of the quickly growing infant. After this period, the milk is largely classified as mature. While the most dramatic compositional changes occur during the first four to six weeks postpartum, the composition remains relatively stable thereafter, with only subtle shifts occurring throughout the remainder of the lactation period [3].

The mean macronutrient composition is characterized by lactose at the highest concentration (6.7-7.8 g/dL), followed by fat (3.2-3.6 g/dL), and the lowest concentration being protein (0.9-1.2 g/dL). The energy density of this milk is estimated at 65-70 kcal/dL, a value that is closely linked to its lipid concentration. It is crucial to note that the macronutrient profile of preterm milk differs, typically exhibiting higher concentrations of both protein and fat than milk produced for term infants [27].

Micronutrient composition in human milk, including vitamins A, D, B1, B2, B6, and B12, and the mineral iodine, exhibits variability that is directly linked to the mother's nutritional status. The levels of these components reflect the mother's current diet and her existing systemic reserves [28,29].

Beyond simply meeting the infant's energy requirements, human milk delivers a complex array of bioactive and immune components. These crucial factors, including antibodies, various immunoglobulins, the antimicrobial proteins lactoferrin and lysozyme, microRNAs, white blood cells (WBCs), and growth factors that are vital for fortifying the developing infant's immune system and offering essential protection against pathogenic threats [30].

3. Breast Milk Benefits

3.1. Effect on the Immune System

At birth, the immune system of a newborn is immature, undergoing its most rapid development during the first two years of life. Specifically, a newborn's immune system has a limited capacity to generate immunoglobulins and B lymphocytes and relies on its systemic cell-mediated immune response. This deficiency, compounded by delayed neutrophil activity, makes newborns highly susceptible to bacterial infections. Furthermore, other immune components are also insufficiently produced, such as complements, interferon-gamma (IFN γ), sIgA, interleukins (ILs), tumor necrosis factors (TNFs), lactoferrin, and lysozyme [8]. Consequently, the immunomodulatory factors in human breastmilk aid the development of the mucosal and systemic immune defenses [31,32].

Human breastmilk provides a substantial amount of 10^8 maternal WBCs each day during early lactation [12]. Approximately 80% of them are macrophages that can move from the bloodstream through the mammary gland epithelium and into the milk. These mononuclear leukocytes are highly functional, acting as macrophages through phagocytosis and later differentiating as dendritic cells that stimulate the T cell activity. Thus, this process offers powerful defenses against pathogens [33].

Cytokines are also present in human milk and influence the immune system. TNFa, IL-6, IL-8, INF γ are some proinflammatory cytokines that, even though they exist in small quantities and decrease with time, retain the capacity to recruit neutrophils and enhance the development of the intestinal mucosa [5]. IL-8 defends against tissue injury induced by TNFa, while INF γ promotes the T helper 1 (Th1) inflammatory and inhibits T helper 2 (Th2) allergic response [34–36].

Fundamental role in the immune system have the maternal antibodies that support the adaptive immunity of the newborn [13]. The most abundant one in the breast milk is sIgA, which facilitates the recognition of foreign antigens by binding to them and forming complexes. These complexes are then absorbed by dendritic cells within the intestinal wall [14]. Regarding other Immunoglobulins, IgG and IgM are in very low amounts, with IgG increasing with time [37].

Lactoferrin, the second most concentrated protein in human milk, is an iron-binding glycoprotein with diverse immune functions. This protein exhibits potent antimicrobial and anti-infectious properties, linked to a preventative role against neonatal sepsis, diarrhea, and NEC. Lactoferrin concentrations are significantly higher in colostrum (7 ng/L) than in mature milk (2–4 g/L) [9,10,38].

Lysozyme, an active enzyme found in exceptionally high concentrations in breast milk, defends against bacteria through multiple mechanisms. It lyses Gram-positive bacteria by breaking down proteoglycans on the cell surface. Additionally, it exhibits a synergistic effect with lactoferrin against Gram-negative bacteria, through pores created by lactoferrin and by digesting the inner cell membrane proteoglycans [11].

3.2. Effect on Growth

Among the bioactive substances in human milk, growth factors are critical, primarily serving to promote the newborn's physical development by stimulating the proliferation and differentiation of their immature cells. Highly significant growth factors detected in breast milk are the vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), glucagon-like peptide-1 (GLP-1), epithelial growth factor (EGF), and insulin growth factors (IGFs) [39].

EGF plays a critical role in facilitating the maturation and subsequent healing of the intestinal lining. Its protective functions within the infant intestine are diverse, encompassing the suppression of the programmed cell death and the correction of the tight junction protein abnormalities in the intestine and liver caused by TNFa [40]. HB-EGF is recognized as the principal growth factor responsible for resolving tissue damage after hypoxia, ischemia-reperfusion injury, hemorrhagic shock, and NEC [17]. The amount of this factor is higher in colostrum and then gradually declines [3].

IGFs are also found abundantly in the early milk and are associated with greater outcomes for preterm infants. Early breastmilk feeding is correlated with higher levels of IGF-1 in serum that helps mitigate several developmental and functional abnormalities. That includes complications like intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and NEC [41]. Additionally, there is a correlation between higher infant weight gain and milk high in IGF-1 [42].

VEGF is an important factor that regulates angiogenesis and is highly associated with ROP. Its negative regulation and insufficient amount lead to dysregulated vascularization of the retina [43,44].

Besides these growth factors, several hormones also influence infant growth and body composition, including leptin, ghrelin, adiponectin, and insulin [45]. Leptin and insulin in breast milk are linked with lower body mass index (BMI) for age and are inversely associated with fat mass deposition [21,46]. In contrast, ghrelin and adiponectin act on the hypothalamus and stimulate hunger [47].

3.3. Effect on Gut Microbiome

Human milk is considered the first probiotic food for the infant [19]. It contains more than 200 bacterial species that are vital for the early colonization and modulation of the gastrointestinal microbiota [20]. The bacterial population is diverse, consisting of *Streptococcus*, *Staphylococcus*, *Bifidobacterium*, *Lactobacillus*, *Propionibacterium*, *Enterococcus*, and *Enterobacteriaceae*. It is estimated that infants ingest as many as 8×10^5 bacteria every day, representing the second most important source of microbes following the birth canal exposure in vaginal deliveries [55]. The microbiota transferred through breast milk assumes an even more beneficial and critical role in preterm infants, particularly those with very low birth weight, due to their substantial risk of infection and adverse short- or long-term health complications [56].

Recent findings define breast milk as a supplier, not only for bacterial microbiome but also the virome [57]. This is generally considered safe and beneficial, inhibiting the transition of pathogenic viral strains [58]. Furthermore, the bacteriophages within the virome play a key role in modelling the bacterial microbiome by encouraging the proliferation of beneficial bacteria and eliminating harmful ones [59].

HMOs constitute the third most abundant component in human milk. Although they offer no direct nutritional value, they are vital modulators of both the developing gut microbiota and the infant's immune system [60]. HMOs protect by binding to pathogens as an alternative target and thus decreasing their adherence to the host's mucosal surface [61]. In addition to that, these oligosaccharides strengthen the gastrointestinal tract and modulate the immune system by influencing gene expression in intestinal epithelial cells [62]. They exhibit significant quantitative and qualitative variability, starting at the highest in colostrum (15-23 g/L) and decreasing in mature milk (1-10 g/L) [60].

Breast milk lipids, notably omega-3-polyunsaturated fatty acids, can also alter the gut microbes in addition to modulating immune cell migration and interfering with gene expression. They can also influence the Th1 and Th2 immune cell response and change the cellular membrane domain, increasing the levels of arachidonic acid [63].

3.4. Effect on Necrotizing Enterocolitis

Necrotizing enterocolitis is a severe condition predominantly affecting preterm neonates, with its incidence inversely correlated to gestational age [48]. Up to 5% of all preterm infants, and as many as 10% of extremely preterm neonates, develop NEC, resulting in a mortality rate exceeding 10% [49]. Survivors frequently face long-term gastrointestinal complications, including short bowel syndrome, cholestasis, liver disease, and chronic feeding problems [50,51]. The underlying pathophysiology of NEC is significantly driven by the immaturity of the infant's gastrointestinal tract, together with a disruption of the normal enteric microbiome (dysbiosis) [52,53]. Immune dysregulation in association with microbial dysbiosis. The microbial profile linked to NEC is defined by a decrease in phyla

Bacillota and *Bacteroidota*, coupled with an increase in *Pseudomonadota*, particularly the *Enterobacteriaceae* group. As the dominant Gram-negative bacteria in the preterm gut, *Pseudomonadota* are hypothesized to stimulate intense proinflammatory immune responses via Toll-like-receptors 4 signaling. This mechanism is believed to lead to the breakdown of the intestinal barrier, ischemia, and subsequent tissue necrosis in susceptible preterm infants [54].

HMOs are thought to significantly reduce this risk by modulating the gut microbiota and immune system. Their protective actions include serving as prebiotics, possessing antiadhesive and antimicrobial properties, and influencing the development of the intestinal epithelial cells and immune responses [16].

HB-EGF, despite its lower concentration in human milk, is recognized as the principal factor responsible for intestinal tissue repair. Its specific actions include stimulating the maturation of the enteric nervous system and simultaneously shielding that system from NEC-induced injury [18].

3.5. Atopy

Children who are breastfed show decreased risk for allergic diseases. Particularly, the incidence of asthma, allergic rhinitis, atopic dermatitis, and wheezing is significantly lower in comparison to infants who are fed with formula [24].

The concentration of cytokines in breast milk significantly affects its immunogenicity. The high levels of IL-4, IL-5, and IL-13, especially in atopic mothers, drive the IgE synthesis and the eosinophilic response [64]. Conversely, Transforming Growth Factor beta, which is a dominant cytokine in human milk, enhances the infant's capacity to generate IgA antibodies against common dietary proteins such as casein, beta-lactoglobulin, gliadin, and ovalbumin [65]. Furthermore, high levels of CD14 may protect against allergy development by inducing a Th lymphocyte response to bacteria [66].

HMOs may also contribute to this. Allergic diseases frequently emerge in newborns due to the dominance of the Th2 cells [67]. The immune system has to shift towards Th1 cells regulation to achieve a balanced immunologic response and effective immune protection [68]. Oligosaccharides can support this by facilitating optimal epithelial maturation and promoting healthy microbial colonization [69,70].

The presence of antioxidants and lipids in the diet elicits complex and varied mechanisms that influence both immune regulation and inflammation. Evidence suggests these compounds have a probable positive correlation with indicators of atopic disease and asthma [71]. Generally, antioxidants are important for the newborn's protection against diseases, and human milk does have an antioxidant capacity [72]. Nutritional antioxidants like Vitamin C and Vitamin E, which are also found in breastmilk, play a protective role against asthma and atopy [73,74].

3.6. Effect on Cancer

Human milk is a great source of microRNAs, small non-coding RNAs that are able to influence the post-transcriptional level of gene expression [45]. There is a great focus on their potential effect in cell proliferation, inflammation, immunomodulation and carcinogenesis. In oncology, the micro RNAs are involved as onco-suppressors, oncogenes and biomarkers helpful not only for diagnostic as well as for therapeutic targets [75–77].

In addition to that, there is an important correlation between breastfeeding and its duration with the decreased incidence of a specific type of cancer in neonates.

Leukemia, including both Acute Myeloid Leukemia (AML) and Acute Lymphoid Leukemia (ALL), is one of the important ones that was found to be low of risk in infants that were breastfed for more than 6 months [25]. Comparing no breastfeeding or < 6 months period of breastfeeding infants with any breastfeeding infant for ≥ 6 months, it was positively correlated with decreased risk (up to 20%) regarding childhood leukemia [26].

Neuroblastomas and Rhabdomyosarcomas were also associated with decreased incidence of leukemia in children who were breastfed for ≥ 12 months [78,79]. Reduced risk has also been observed

with Retinoblastomas, however breastfeeding for more than 12 months doesn't seem to offer additional benefits [80].

3.7. Other Benefits

3.7.1. Inflammatory Bowel Disease

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are rapidly increasing global health concerns with high pediatric prevalence rates [81]. In Europe and the majority of North America, the pediatric-onset UC stands at 1 to 4 per 100,000 per year [82]. Reports suggest that breastfeeding may reduce the prevalence of both CD and UC. This protective effect is achieved by human milk's capacity to shield the infant from gastrointestinal infections, stimulate the development and growth of the gastrointestinal mucosal system, and enhance the immune system's ability to recall and respond to pathogens [83–85].

3.7.2. Celiac Disease

Breastfeeding during the initiation of dietary gluten intake has been associated with a diminished risk of developing celiac disease in children under the age of 2. Furthermore, maintaining breastfeeding after the initial introduction provided an even greater protective advantage, especially in children who were breastfed for more than six months [86].

3.7.3. Gastrointestinal Infections

The risk of acute gastroenteritis in infants is significantly decreased with increased breastfeeding duration. Infants breastfed for over 12 months had fewer instances of gastroenteritis compared to those breastfed for shorter periods. The protective effect also includes exclusive breastfeeding during the first six months, suggesting that both early exclusivity and sustained duration provide substantial defense against this infection [87].

3.7.4. Metabolic Health

The cumulative duration of breastfeeding is a critical determinant of its metabolic advantages. With an average duration of nine months, the protective impact against metabolic risk factors becomes significantly more evident, leading to a lowered incidence of metabolic syndrome. These protective effects encompass a reduced likelihood of adverse findings such as low HDL-C, high triglycerides, and high blood sugar [22]. Specifically, breastfeeding for more than six months is significantly linked to a reduced risk of late-onset Type 2 Diabetes [23].

4. Discussion

The scientific understanding of human breast milk has evolved significantly, shifting from a focus on macronutrient sufficiency to an appreciation of breastmilk as a complex, bioactive signaling system. This review highlights that human milk functions as a sophisticated physiological bridge, compensating for the transient immunologic and gastrointestinal immaturity of the neonate while simultaneously programming long-term metabolic health.

The relevance of these findings is further highlighted by the current human milk research that involves rigorous clinical trials registered in international databases that aim to further elucidate the benefits of human breast milk.

A significant portion of ongoing research is dedicated to optimizing human milk for the preterm newborns. Trials such as N-forte [88] and ENACT+ [89] evaluate how to balance the bioactivity of breastmilk with the high macronutrient requirements of extremely low birth weight infants, aiming to refine fortification to maximize growth and neurodevelopmental outcomes [90–92].

Additional active studies explore the specific influence of maternal health on milk composition and subsequent infant gut colonization and microbiome [93,94]. Researchers are isolating the effect

of specific bioactives, like the direct correlation between human milk and HMOs and the incidence of infantile colic and atopic dermatitis in term infants [95].

Finally, foundational work continues regarding the milk composition, such as the aim to map the structural changes of breast milk over the first full year of lactation [96].

Collectively, these trials underscore a scientific commitment to continue the research on the complexity of human milk and its benefits, and develop in the future personalized nutritional therapies that can replicate the specific metabolic and immunologic benefits

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Abbreviations

ALL	Acute Lymphoid Leukemia
AML	Acute Myeloid Leukemia
AAP	American Academy of Pediatrics
BPD	bronchopulmonary dysplasia
CD	Crohn's disease
EGF	epithelial growth factor
GLP-1	glucagon-like peptide-1
HB-EGF	Heparin-binding growth factor
HGF	hepatocyte growth factor
HMOs	Human milk oligosaccharides
IBD	Inflammatory Bowel Diseases
IFN γ	interferon-gamma
IGFs	insulin growth factors
ILs	interleukins
NEC	necrotizing enterocolitis
ROP	retinopathy of prematurity
sIgA	secretory immunoglobulin A
Th1	T helper 1
Th2	T helper 2
TNFs	tumor necrosis factors
UC	Ulcerative colitis
VEGF	vascular endothelial growth factor
WBCs	white blood cells
WHO	World Health Organization

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