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Human Breast Milk as a Living Therapeutic System: Translational Implications for Neonatal Health

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ABSTRACT

The use of human breast milk is gaining new recognition as more than just nutrition and as a multifaceted, dynamic, and biologically active environment with essential treatment effects in neonatal health. In addition to macronutrients, it has a variety of bioactive factors such as immunoglobulins, human milk oligosaccharides, antimicrobial peptides, cytokines, growth factors, microbiota, extra-cellular vesicles and microRNAs which, in combination, promote immune maturation, gut and brain development, metabolic programming and defense against infectious diseases and inflammatory diseases. This review summarizes the existing literature which conceives breast milk as a living therapeutic system with high level of translational application to the care of the neonatal population. We discuss mechanistic pathways by which breast milk has an impact on immune regulation, gut-microbiome interactions, neurodevelopment and long-term disease risk reduction, which are necrotizing enterocolitis, sepsis, allergic conditions, and metabolic disorders. New translational evidence that reveals the effects of breast milk-derived bioactive as natural immunomodulators, postbiotics, and epigenetic regulators is mentioned. The review also discusses clinical implications of vulnerable groups like preterm and low-birth-weight babies, as well as the issue of breast milk use, formula supplementation, and inequity in breastfeeding. This review brings together molecular biology, clinical neonatology, and translational nutrition science and emphasizes the importance of breast milk as a platform of early-life precision health and as a paradigm of the next generation of nutrition and therapeutic approaches.

Keywords: Human breast milk, neonatal health, immune programming, microbiome, translational nutrition, bioactive milk components.

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INTRODUCTION

It has been established that human breast milk is the best source of food to be given to the newborn baby; nevertheless, there is emerging scientific data that it serves more than just as nourishment. Modern studies are moving towards the notion that breast milk is a dynamic, bioactive, and living therapeutic system, which actively determines the immune system of the neonatal, developmental, and long-term health outcomes. Instead of being a fixed biological fluid, breast milk is made flexible to respond to maternal, environmental and infant-specific cues, providing specific biological messages at the most vital stage of early-life development.⁽¹⁾

Neonatal period is a period of increased vulnerability, which is an immaturity of immune responses, insufficient gut barriers, and rapidly developing metabolic and neurological systems. At this stage, the breast milk contains not only macronutrients and micronutrients, but also a complex of immunological and regulatory elements, such as immunoglobulins, antimicrobial peptide, cytokine, human milk oligosaccharide (HMOs), growth factor, microbiota, extra cellular vesicles and microRNAs. These elements work together to facilitate immune development, create a healthy gut microbiome, neurodevelopment, and inflammatory and infectious diseases.⁽²⁾

Regarding the application in the context of translation, the interpretation of breast milk as a living therapeutic system has a significant implication on the care of neonates. The breastfeeding has always been linked with low rates of neonatal sepsis, enterocolitis, respiratory infections, allergic diseases, as well as metabolic disorders later in life. The effects of breast milk as a natural immunomodulator and biological defense system are especially important in preterm and low-birth-weight babies. Although the infant formula has been improved with time, the design has not reached the level of biological complexity and functional variability that is found in human milk.⁽³⁾

This review seeks to compile existing evidence in human breast milk in upholding the notion of human breast milk as a living therapeutic system, both in terms of bioactive composition, mechanistic pathways, and translational applicability to the health of the neonate. The review synthesizes molecular biology, immunology, microbiome science, and clinical neonatology to connect the role of the biological signalling induced by breast milk in early-life protection and developmental programming, which can be useful in introducing new approaches to precision neonatal nutrition and subsequent therapeutic approaches. The concept of the human breast milk as a living therapeutic system incorporating immune, microbial, neurodevelopmental, and metabolic signalling pathways is shown in figure 1.

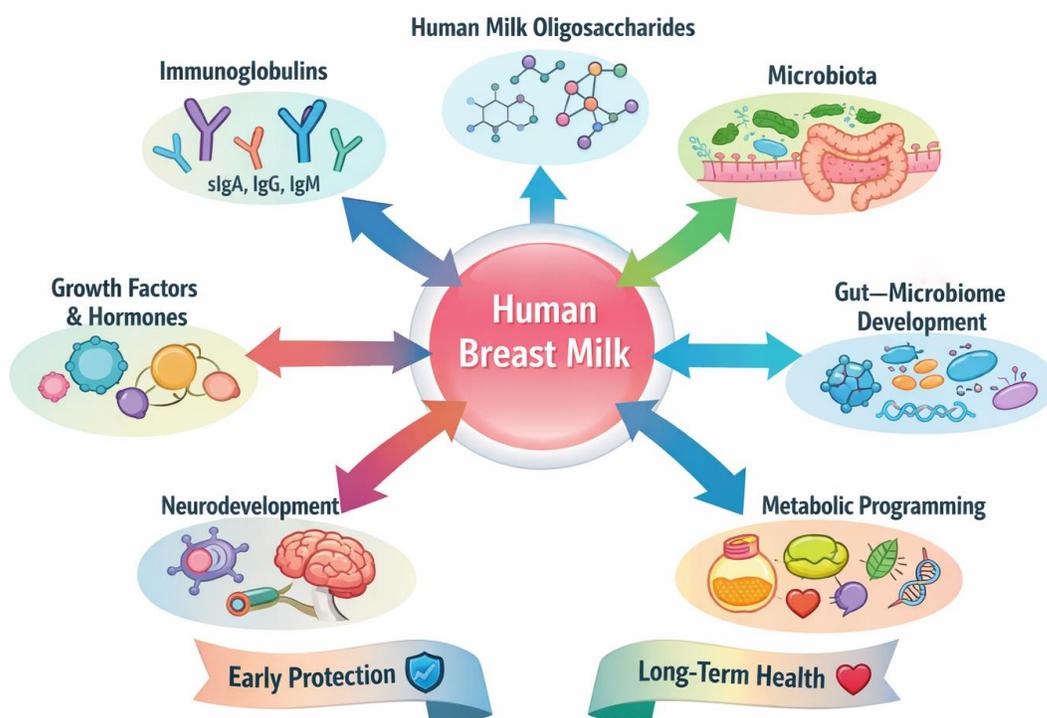


Figure 1: Human Breast Milk as a Living Therapeutic System

Biological Complexity of the Human Breast Milk:

Human breast milk, in particular, is a highly composite and vibrant living fluid whose composition is not a constant factor but a variable one continually changing along with and in response to the infant's physiological needs at different ages. Breast milk is not homogenous like man-made nutrients, its variety changes depending on the lactation period, the woman and, sometimes, even the moment of the day or hour. In early development, it has been demonstrated that colostrum, transitional milk and mature milk have significant differences in the levels of immunological, growth factor and metabolic regulators, indicating that breast milk is adaptive.⁽⁴⁾

Many factors of the maternal genetics, nutrition, health conditions, microbiome composition, environmental exposures, and gestational age at delivery affect the composition of breast milk. Indicatively, the milk of mothers of preterm babies contains elevated levels of immunoglobulins, lactoferrin and anti-inflammatory determinants, which indicate a biologically individualized reaction to neonatal susceptibility. This modulation of adaptation highlights the fact that breast milk is an adaptive and responsive therapeutic system, but not a passive source of nutrition.⁽⁵⁾

Breast milk at the molecular level is composed of a complicated mixture of bioactive compounds that orderly interact with each other. These are immune cells, antibodies, antimicrobial peptides, enzymes, hormones, cytokines, chemokines, oligosaccharides, commensal bacteria, and

extracellular vesicles containing microRNAs that regulate. The presence of these components creates one biological network, which together contributes to immune education, taking care of tissues and controlling metabolism. This is a characteristic of the therapeutic potential of breast milk in such systems-level complexity.⁽⁶⁾

Notably, breast milk is real-time responsive to cues of infants. It has been shown that the composition of maternal milk can vary in reaction to infant infection or inflammation with more immune mediators and protective proteins. The fact that this is a two-way communication between mother and infant strengthens the notion that breast milk is a living system that has the ability to sense and act in accordance with biological needs.

Breast milk temporal variability and functional plasticity has important translational neonatal health implications. The breast milk can provide stage specific and context specific protection during critical periods of immune and organ development due to this biological plasticity. On the contrary, the infant formulas are rather stable and do not have the capability of replicating this biological responsiveness. This complex nature of breast milk composition, then, is critical to the future of neonatal nutrition approaches, the enhancement of donor milk-feeding, as well as in the understanding of the development of bioinspired therapeutic interventions.⁽⁷⁾

BREAST MILK BIOACTIVE COMPONENTS AND MECHANISMS OF ACTION:

The human breast milk is governed by a broad range of bioactive factors, which altogether play a role in neonatal protection and development programming. These elements have complementary and overlapping effects, in favour of immune development, microbial homeostasis, tissue development, and metabolic control. Their significance in detail as mechanistic is a key to understanding breast milk as a living therapeutic system.⁽⁸⁾ Table 1 summarizes the major bioactive components present in human breast milk and highlights their diverse biological functions, emphasizing their synergistic roles in supporting neonatal immunity, gut maturation, neurodevelopment, metabolic programming, and long-term health outcomes.

Table 1: Bioactive Components of Human Breast Milk and Their Biological Functions

Bioactive Component	Examples	Primary Biological Function	Clinical Relevance
Immunoglobulins	sIgA, IgG, IgM	Passive immunity, mucosal protection	Reduces infections, NEC
HMOs	2'-FL, LNT	Prebiotic, immune modulation	Microbiome shaping
Antimicrobial proteins	Lactoferrin, lysozyme	Antimicrobial, anti-inflammatory	Sepsis prevention
Growth factors	EGF, IGF	Gut maturation, tissue repair	Preterm gut protection
Hormones	Leptin, adiponectin	Appetite & metabolic regulation	Obesity risk reduction
Extracellular vesicles	miRNAs, exosomes	Epigenetic regulation	Immune programming

Immunological Components

One of the most important protective components of breast milk are immunological ones. Secretory immunoglobulin A (sIgA) takes a central role since it is used to coat mucosal surfaces and prevent adhesion of pathogens without causing inflammatory reactions. Other antibodies such as IgM and IgG also augment passive immunity in the early neonatal stage when the ability of endogenous response is constrained. The multifunctional iron-binding glycoprotein Lactoferrin has potent antimicrobial, antiviral, anti-inflammatory effects along with enhancing intestinal epithelial proliferation.⁽⁹⁾ Immune tolerance Cytokines and chemokines which are found in breast milk, including interleukin-10 and transforming growth factor- β , control immune tolerance and inhibits uncontrolled inflammation, which subsequently mitigates the risk of immune-mediated disease.

Human Milk Oligosaccharides

Human milk oligosaccharides (HMOs) are carbohydrates that are structurally complex, specific to human milk and a major stimulus of neonatal gut and immune development. HMOs can selectively stimulate the development of beneficial intestinal microbes, especially species of Bifidobacterium, which form a protective microbial ecosystem although the infant cannot digest them. HMOs are also decoy receptors, which prevent the binding of pathogens to intestinal epithelial cells, and directly mediate immune signalling events. There is also growing evidence indicating that HMOs can impact on systemic immunity and can even lead to long-term prevention of allergic and metabolic diseases.⁽¹⁰⁾

Miltein Breis sulficida Breast Milk Microbiota and Antimicrobial Factors

Breast milk is a source of vertical transmission of maternal microbiota, which inoculates commensal bacteria that settle on the intestines of the newborn. These microbes are very important in immunological education, intestinal barrier development and metabolic homeostasis. Simultaneously, antimicrobial peptides (defensins, lysozyme, cathelicidins) ensure protection against microorganisms immediately and avoid harm to microbial communities. Such an antimicrobial balance is critical towards the prevention of dysbiosis and other related inflammatory disorders, especially in preterm babies.⁽¹¹⁾

Growth Factors, Hormones and Metabolic Regulators

Breast milk has several growth factors present such as epidermal growth factor, insulin-like growth factors, and vascular endothelial growth factor that support various processes such as intestinal maturation, blood vessel formation, and tissue repair. Besides, certain hormones (leptin, adiponectin, insulin, and ghrelin) are involved in the control of the appetite, energy balance, and

metabolic programming. The bioactive molecules are involved in normal growth patterns and could minimize the risk of metabolic syndrome and obesity in the long run.⁽¹²⁾

The MicroRNAs and Extracellular Vesicles

In the recent developments, the existence of extracellular vesicles, such as exosomes, in breast milk has been emphasized. MicroRNAs, among other regulatory molecules, are contained in these vesicles and can withstand gastrointestinal digestion and enter into the systemic circulation. MicroRNAs of breast milk have been attributed with roles of immune control, epithelial differentiation and regulation of gene expression.⁽¹³⁾ This is an epigenetic layer of regulation that highlights the importance of breast milk on shaping neonatal development on a molecular level and is a new area of frontier in trans-disciplinary neonatal studies.

These bioactive components together are considered to form a complex biological system that sends integrated signalling's helping to regulate neonatal immune development, microbial colonization and developmental programming. This is due to their synergistic effects that make breast milk superior to artificial substitutes and make it a natural and evolutionarily optimized therapeutic intervention of first life.

Neonatal Dynamics of Immune and Gut Development Moved by Breast Milk:

There is rapid maturation in the neonatal immune and gastrointestinal systems in the first stages of life, but both are not functionally mature at birth. The role of breast milk in directing this developmental process is essential in terms of offering immunological protection to the neonatal immune system at the same time educating the neonatal immune system. Breast milk promotes host defense via a well-coordinated immune activation and tolerance response that does not result in overproduction of inflammatory responses, especially in the susceptible state of the neonatal stage.⁽¹⁴⁾

Breast milk helps in immune maturation provision of passive immunity and immune-modulatory cues. The intestinal lining is protected by secretory immunoglobulin A, which also blocks the attachment and movement of pathogens while allowing the exposure of non-pathogenic antigens necessary for the immune system's learning process. The latter process is made possible by the anti-inflammatory cytokines such as transforming growth factor- β and interleukin-10, which induce immune tolerance and prevent the immune system from being wrongly activated, thus lowering the chances of one developing allergies and autoimmune diseases.⁽¹⁵⁾ In addition, the immune cells and soluble factors found in breast milk interact with the immune tissues of the infants, which is advantageous for the development of both the innate and adaptive immune responses. Key breast milk components and their specific effects on neonatal immune system

maturation and gastrointestinal development are summarized in Table 2, which demonstrates the roles of these biological active factors in immune tolerance, gut barrier integrity enhancement, and healthy microbial colonization support during the newborn period.

Table 2: Breast milk components, effects on neonatal immune development and gastrointestinal development.

Breast Milk Component	Target System	Biological Effect	Health Outcome
sIgA	Gut mucosa	Pathogen exclusion	Reduced GI infections
HMOs	Gut microbiome	Bifidobacteria growth	Microbial balance
Lactoferrin	Immune cells	Anti-inflammatory	Lower NEC risk
Growth factors	Intestinal epithelium	Barrier maturation	Reduced permeability
Cytokines (TGF- β , IL-10)	Immune regulation	Immune tolerance	Allergy prevention

The digestive tract acts as a hub point of nutrition, immunity and microbial colonization. Breast milk facilitates the maintenance of gut barrier by supporting the maturation of epithelial cells, formation of tight junctions and repair of mucosa. The growth factors including epidermal growth factor and insulin-like growth factors hasten the development of the intestine and decrease intestinal permeability, which inhibits bacterial translocation and system inflammation. The effect becomes particularly severe in the case of preterm babies, which have inadequate gut barrier and are highly vulnerable to inflammatory damage.⁽¹⁶⁾

Another pillar of the gut development by breast milk is microbiome establishment. The oligosaccharides present in human milk, on the one hand, act as selective and preferential nutrients to the beneficial niches of microbes, predominantly to the Bifidobacterium and Lactobacillus species, thus creating a microbial community that is in favor of immune homeostasis. On the other hand, the same or similar mechanisms are through which antimicrobial peptides and lactoferrin put a stop to the proliferation of pathogens but at the same time allow the commensal bacteria to survive. This microbial equilibrium boosts colonization resistance and decreases the occurrence of gastrointestinal as well as systemic infections.⁽¹⁷⁾

Immune and gut development via the presence of breast milk is closely linked to the decrease in the likelihood of neonatal illnesses, including necrotizing enterocolitis (NEC), late-onset sepsis, and inflammatory bowel disorders. The clinical trials always prove the reduced incidence of NEC and a higher survival rate of breastfed preterm infants over formula-based infants. These preventive effects underscore the role of breast milk as a natural immunotherapy agent especially in intensive care units of neonatal care.⁽¹⁸⁾

Altogether, breast milk coordinates a developmental program involving immune education, maturation of gut and microbial symbiosis. Breast milk is a living therapeutic system that prepares early-life immune and gastrointestinal development to provide resilience against infections and

inflammatory diseases and solidifies its position as a living therapeutic system with far-reaching translational implications on neonatal health.

Breast Milk and Neurodevelopment and Metabolic Programming of Neurodevelopment:

Nutrition in early life is determinant in the development of neurodevelopmental and metabolic pathways and breast milk is the source of important biological cues in this delicate developmental period. In addition to energy providers, breast milk provides neurotrophic, hormonal, and epigenetic factors which affect brain development, cognitive growth and long-term metabolic wellbeing.⁽¹⁹⁾

Breast milk promotes neurodevelopment in a variety of ways. Polyunsaturated fatty acids, especially docosahexaenoic acid (DHA) and arachidonic acid (ARA) are required in the neuronal membrane formation, synaptogenesis, and visual development. These fatty acids are fast in building up within the brain during infancy and have been linked to better cognitive and visual performance of breastfed infants. Also, brain-derived neurotrophic factor and nerve growth factor growth factors are present in breast milk and assist the differentiation and survival of the neurons as well as their connection.⁽²⁰⁾ There is also new evidence that breast milk-related microRNAs and extracellular vesicles play a role in neural gene regulation and synaptic plasticity which underlines an epigenetic aspect of neurodevelopmental programming.

Another important field that is affected by breast milk is the metabolic programming. The presence of hormones and bioactive peptides in breast milk such as leptin, adiponectin, insulin and GHrelin has a regulatory effect on appetite control, energy regulation and insulin sensitivity. The exposure to these signals in the infancy period may affect adipocytes development, metabolism of glucose, and body structure in the long term.⁽²¹⁾ The epidemiological evidence indicates a consistent reduction in the risk of childhood obesity, diabetes type 2 and metabolic syndrome in later adult life in individuals breastfed, which implies a protective metabolic imprinting effect.

The indirect effects of breast milk on neurodevelopment and metabolism are also via effects on the gut-brain axis. Through the establishment of a positive gut microbiome, breast milk has a role to play in effects on microbial metabolite production, immune signaling and neuroendocrine pathways that influence brain functioning and behaviour. The neural development, immune homeostasis, and metabolic homeostasis have been attributed to short-chain fatty acids produced by milk-stimulated microbiota.⁽²²⁾ Fig. 2 illustrates how the nutrients, hormones and epigenetic

factors that are carried by breast milk influence neurodevelopmental and metabolic processes.

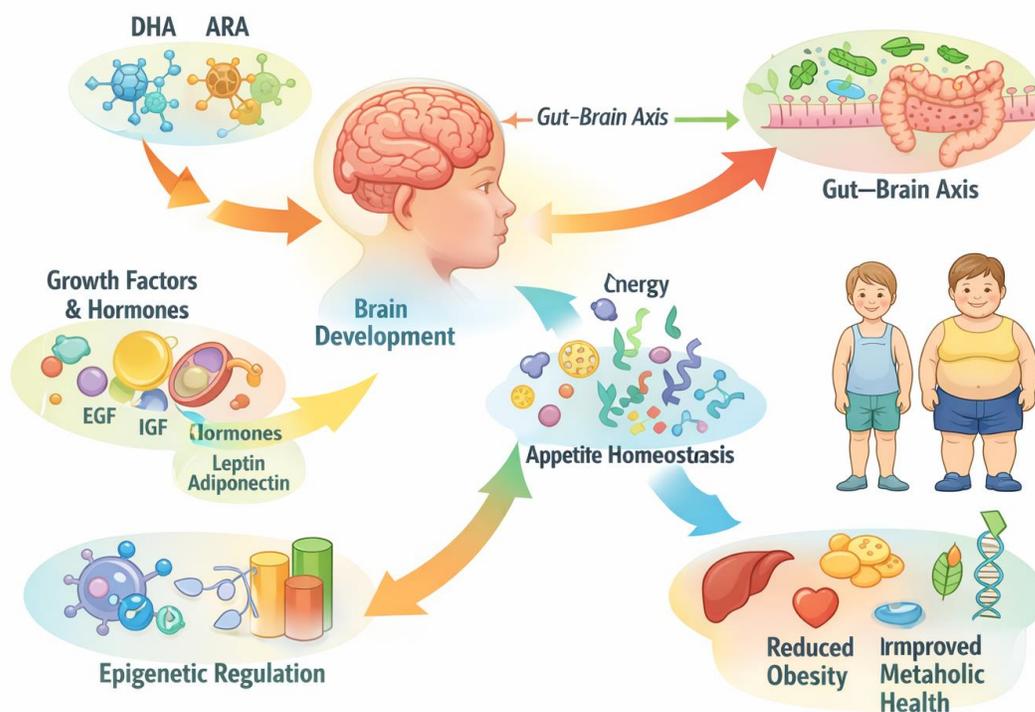


Figure 2: Neurodevelopment and Metabolic Programming mediated by Breast Milk

Neonatal Clinical Care Translational Implications:

The discovery of human breast milk as living therapeutic system is significant in translational clinical practice in neonatal clinical work, especially neonatal intensive care units (NICU). Breast milk is a versatile intervention that controls immunity, develops organs, and decreases disease burden among vulnerable neonates, in addition to being the best nutrition. The application of this knowledge to the clinical care can improve the outcomes of neonatal care and support evidence-based feeding practices.⁽²³⁾

Breast milk offers breast milk essential protection to preterm and low-birth-weight babies against life-threatening illnesses like necrotizing enterocolitis, late-onset sepsis, and pneumonia. The clinical practice does shift towards the use of mother own milk in the first line of feeding, and donor human milk is the next option when the first one is not available. Most of the immunological and bioactive properties are still present in donor milk, despite the possibility of some being eliminated due to processing by methods like pasteurization. One of the most important challenges is the optimization of the donor-milk handling and fortification approaches.⁽²⁴⁾ Table 3 highlights the translational and clinical implications of breast milk in neonatal care, demonstrating how its bioactive components inform preventive, therapeutic, and supportive strategies to improve

neonatal immunity, gastrointestinal health, neurodevelopment, and overall clinical outcomes.

Table 3: Breast Milk Translational and Clinical Implications in Neonatal Care

Neonatal Population	Breast Milk Benefit	Clinical Outcome
Term infants	Immune maturation	Reduced infections
Preterm infants	Gut protection	Lower NEC incidence
Low birth weight infants	Anti-inflammatory effects	Reduced sepsis
NICU infants	Microbiome stability	Improved survival
Formula-fed substitutes	Limited bioactivity	Higher disease risk

Preterm babies usually have high nutritional requirements, which require breast milk fortification to satisfy them. Translational research is taking a new direction of individualized fortification methods which maintains the bioactivity and provides sufficient growth. New ideas like precision nutrition are trying to customize fortification on the basis of milk composition, infant needs, and developmental stage that conform to clinical practice and the biological adjustability of breast milk.⁽²⁵⁾

In addition to direct feeding, the breast milk-derived products have the potential of being used as translational models in terms of natural biotherapeutics. Single bioactive such as lactoferrin, HMOs, and extracellular vesicles are currently considered in neonatal care as an option of therapeutic supplementation. Such interventions can offer specific immune and gut protection in infants that lack access to adequate breast milk.⁽²⁶⁾

Public health as part of the strategy to promote the health of newborns, breastfeeding and equitable access to human milk are key elements. Pharmacists and clinicians are crucial in assisting the health care profession in the support of breast feeding, family counselling, and incorporating translational evidence in the neonatal care procedures. The therapeutic lens of breast milk strengthens its core role in the healthcare of infancy and childhood and leads to the necessity of the policies of protection, promotion, and support of breastfeeding.⁽²⁷⁾

Difficulties, Moral Implications and Future Projections:

Although the advantages of human breast milk are well established, there are a number of issues that make it difficult to use it as a therapeutic aid in the treatment of newborns. Socioeconomic and cultural factors, insufficient maternity support, and insufficient breastfeeding education are all factors that cause inequities in breastfeeding initiation and continuation, especially in the low- and middle-income contexts where access to lactation support and donor milk services is still restricted.⁽²⁸⁾

The administration of donor human milk has ethical and logistical issues associated with safety, availability and processing. Although pasteurization is paramount in protecting against microbes, it can cause degradation of heat sensitive bioactive agents which are enzymes, immunoglobulins,

extracellular vesicles among others. The issue of balancing microbial safety and maintenance of biological functionality has been a major issue in human milk banking, with issues of commercialization and informed consent and equitable distribution.⁽²⁹⁾

The scientific gaps still remain even after discovery of breast milk bioactive. Most components and their effects, particularly in the long term, have not been well studied, which limits their translational use. The future study needs to focus on precision neonatal nutrition that incorporates maternal, milk composition, and infant-specific needs. Omics technology development, bioinspired formula development, targeted supplementation and optimized donor milk processing can assist in maintaining the therapeutic properties of human milk and facilitate fair and evidence-based neonatal health policies.⁽³⁰⁾

CONCLUSION

Human breast milk is much more than a nutritious substrate; it is a biotic system of nutritional sources of biological signals that the human body needs to provide neonatal security and growth. Breast milk facilitates immune maturation, gut integrity, neurodevelopment, and metabolic programming in a sensitive period of early life and is due to its complex and adaptive composition. Combined activities of immunological, microbiota, growth regulator, and epigenetic mediators are unique characteristics of breast milk as an evolutionary optimized intervention in neonatal health. Clinical implications of breast milk research Translational Breast milk have a clinical role especially in preemies and high-risk babies and may strengthen the need to focus more on breastfeeding and human milk-based interventions in paediatric practice. The potential of breast milk biology to enhance the neonatal outcomes is enormous but as an area that is currently underdeveloped in terms of its translation to precision nutrition and therapeutics development. By acknowledging the breast milk as a living therapeutic system, a potent paradigm of clinical practice, research and policy in health promotion is formed in the future.

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