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# THE ROLE OF HUMAN MILK OLIGOSACCHARIDES IN THE DEVELOPMENT OF EARLY GUT MICROBIOTA AND NEONATAL IMMUNITY: A COMPREHENSIVE REVIEW

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## ABSTRACT

Human milk oligosaccharides (HMOs) are the third most abundant solid component of human breast milk and a key bioactive factor in early-life nutrition. This scoping review synthesizes current evidence on the role of HMOs in shaping the infant gut microbiota and supporting neonatal immune development. We searched PubMed, MEDLINE, Scopus, and Web of Science for peer-reviewed original studies, clinical trials, and review articles addressing HMO structure, microbial interactions, and immunological outcomes. The available evidence indicates that HMOs act as selective substrates for beneficial bacteria, particularly infant-type bifidobacteria, while also functioning as soluble decoy receptors that may reduce pathogen attachment to the intestinal epithelium. In addition, microbial fermentation of HMOs produces short-chain fatty acids that contribute to gut barrier integrity and may influence immune regulation. Emerging clinical studies suggest that specific HMO supplementation may support microbiota development and selected health outcomes in infants, although the evidence remains heterogeneous, and more longitudinal studies are needed. Overall, HMOs appear to play an important role in the early development of the gut microbiome and neonatal immunity, but further well-designed studies are required to clarify structure–function relationships and clinical relevance.

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## KEYWORDS

Human Milk Oligosaccharides, Gut Microbiota, Neonatal Immunity, Immunomodulation, Neurodevelopment

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## Introduction

Human milk is a biologically active fluid that provides not only nutrients, but also a wide range of molecules involved in early immune and metabolic development. Among its bioactive components, human milk oligosaccharides (HMOs) are of particular interest because they are the third most abundant solid component of human milk and are not digested by the infant. Instead, they reach the lower gastrointestinal tract, where they may influence microbial colonization and host-microbe interactions in early life.

Current evidence indicates that HMOs act as selective substrates for beneficial bacteria, especially infant-associated *Bifidobacterium* species, thereby contributing to the establishment of a microbiota profile characteristic of breastfed infants. In addition, HMOs may function as soluble decoy receptors that reduce pathogen adhesion to the intestinal epithelium and may support gut barrier integrity through microbial fermentation products such as short-chain fatty acids. Through these mechanisms, HMOs are thought to contribute to the maturation of both innate and adaptive immune responses during a critical developmental window.

Interest in HMOs has increased further with the development of analytical and synthetic methods that allow the study of individual HMO structures and their biological effects. This has created new opportunities to examine how differences in maternal glycosylation profiles may shape infant microbiota composition and downstream health outcomes. However, the available evidence remains heterogeneous, and many structure–function relationships are still insufficiently defined.

The aim of this review is to summarize current knowledge on the role of HMOs in the development of early gut microbiota and neonatal immunity, with particular attention to their structural diversity, microbial effects, and immunological relevance. By synthesizing findings from recent experimental and clinical studies, this review seeks to identify both established mechanisms and key knowledge gaps that should guide future research.

### Methodology

We conducted a scoping review to map the available evidence on the biological and clinical roles of human milk oligosaccharides (HMOs) in early gut microbiota development and neonatal immunity. The review was designed to synthesize findings from experimental, observational, and clinical studies and to identify major themes, mechanisms, and knowledge gaps in the current literature.

The search was conducted across PubMed, MEDLINE, Scopus, and Web of Science using combinations of controlled vocabulary and free-text terms related to human milk oligosaccharides, infant gut microbiota, neonatal immunity, breast milk, infant formula, short-chain fatty acids, and clinical outcomes. Only peer-reviewed publications in English were considered. We prioritized recent studies and included landmark articles that provided foundational information on HMO structure and function.

Studies were screened in two stages. First, titles and abstracts were reviewed for relevance. Full texts were then assessed against the eligibility criteria. We included original research articles, clinical trials, and relevant review papers that addressed HMO structure, microbial colonization, immune development, or clinically relevant outcomes in infants. Studies focusing on unrelated populations or lacking sufficient relevance to the topic were excluded.

Data were extracted from the included studies using a standardized approach focused on study design, population, HMO type or intervention, main microbiological or immunological outcomes, and key conclusions. The findings were then organized thematically to present the evidence in a clear and structured manner. Because this was a scoping review, the emphasis was placed on mapping the literature rather than performing a quantitative meta-analysis.

**Table 1.** Study selection criteria and search strategy

| Item                       | Specification  |
|----------------------------|--|
| Review type                | Scoping review   |
| Databases searched         | PubMed, MEDLINE, Scopus, and Web of Science  |
| Language                   | English  |
| Publication types included | Original research articles, clinical trials, and relevant review articles  |
| Main topic areas           | Human milk oligosaccharides, infant gut microbiota, neonatal immunity, breast milk, infant formula, short-chain fatty acids, and clinically relevant infant outcomes |
| Inclusion criteria         | Studies addressing HMO structure, microbial colonization, immune development, or infant clinical outcomes  |
| Exclusion criteria         | Studies unrelated to the topic, studies in irrelevant populations, and publications lacking sufficient relevance to HMO biology or clinical effects                  |
| Screening process          | Titles and abstracts were screened first; full texts were then assessed against the eligibility criteria   |
| Data extracted             | Study design, population, HMO type or intervention, main microbiological or immunological outcomes, and key conclusions  |

*Caption: Inclusion and exclusion criteria, databases searched, screening process, and data extraction approach used in this scoping review.*

## Results

### Architectural Complexity and Classification

Human milk oligosaccharides (HMOs) are structurally diverse and therefore capable of supporting multiple biological functions. More than 200 distinct HMO structures have been identified in human milk, reflecting the activity of maternal glycosyltransferases during lactation.

HMOs are composed of five major monosaccharides: glucose, galactose, N-acetylglucosamine, fucose, and sialic acid, usually N-acetylneuraminic acid. All HMO structures share a lactose core, to which lacto-N-biose or N-acetylglucosamine units may be added to generate branched and elongated backbones.

These molecules are grouped into three categories based on end modifications and charge. Table 2. shows these groups.

**Table 2.** Classification of common human milk oligosaccharides

|  |   |
|--|---|
| <b>Neutral Fucosylated Glycans</b>     | These structures contain terminal fucose residues attached to the core chain via specific glycosidic linkages. Prominent examples include two-prime-fucosyllactose and three-prime-fucosyllactose.          |
| <b>Acidic Sialylated Glycans</b>       | Characterized by terminal sialic acid residues, these additions impart a negative electrical charge to the molecule. Representative examples include three-prime-sialyllactose and six-prime-sialyllactose. |
| <b>Neutral Non-Fucosylated Glycans</b> | These molecules possess elongated core structures devoid of fucose and sialic acid modifications. Key examples include lacto-N-tetraose and lacto-N-neotetraose.  |

*Caption: Representative structural architectures of fucosylated, sialylated, and neutral-core human milk oligosaccharides.*

For descriptive purposes, HMOs are commonly grouped into three broad classes based on their terminal modifications and charges. Fucosylated HMOs contain terminal fucose residues linked to the core structure through specific glycosidic bonds. Representative examples include 2'-fucosyllactose and 3-fucosyllactose. Sialylated HMOs contain terminal sialic acid residues that confer a negative charge, with 3'-sialyllactose and 6'-sialyllactose as typical examples. Non-fucosylated neutral HMOs include structures such as lacto-N-tetraose and lacto-N-neotetraose.

The HMO profile varies substantially between individuals. One of the main determinants of this variation is maternal secretor status, which depends on the expression of the fucosyltransferase gene. Mothers with an active secretor phenotype produce higher amounts of alpha-1,2-fucosylated HMOs, including 2'-fucosyllactose, whereas non-secretor mothers produce little or none of this structure. Recent high-resolution profiling studies have reported dozens of individual HMOs in a single milk sample, underscoring the extent of natural inter-individual variation and its potential relevance for infant gut colonization.

### Ecological Engineering of the Gut Microbiota

A central biological role of HMOs is to shape the early intestinal microbiota. Because infants do not possess the enzymes needed to digest these complex glycans, HMOs reach the colon largely intact, where they can serve as substrates for selected commensal organisms.

This selective advantage is most evident for infant-associated *Bifidobacterium* species. These bacteria possess specialized gene clusters that enable transport and degradation of HMOs, allowing them to grow efficiently in the breastfed infant gut. In particular, strains such as *Bifidobacterium bifidum* are well adapted to HMO utilization and may therefore contribute to early microbial dominance by bifidobacteria.

The ecological effects of HMOs extend beyond primary fermenters. Several studies suggest that HMO metabolism supports cross-feeding within the microbial community, with partially degraded products and fermentation metabolites becoming available to other bacteria. Short-chain fatty acids, especially acetate, propionate, and butyrate, are among the main downstream products of this process. These metabolites contribute to a lower colonic pH and may support colonocyte metabolism and intestinal homeostasis.

### **Direct and Indirect Orchestration of Neonatal Immunity**

HMOs may also contribute to neonatal immune development through both direct and indirect mechanisms. One widely discussed mechanism is pathogen decoy activity: because some HMO structures resemble glycans on intestinal epithelial surfaces, they may bind microbial adhesins, thereby reducing pathogen attachment to the mucosa. In this way, free HMOs can limit the ability of certain pathogens to colonize or invade the neonatal gut.

Experimental studies further suggest that specific HMOs may influence epithelial barrier function. For example, some models have shown increased expression of mucin-related and barrier-associated genes in intestinal epithelial cells after exposure to selected HMO structures. These findings support the view that HMOs may strengthen the mucosal barrier in addition to acting as soluble decoy receptors.

Evidence also indicates that a proportion of HMOs may be absorbed intact or partially modified across the intestinal epithelium, allowing systemic exposure and potential interactions with immune cells. In this context, HMOs and their metabolites have been proposed to modulate immune signaling pathways involving lectin receptors and pattern-recognition receptors, although the exact molecular pathways remain incompletely defined.

### **Clinical Translation and Synthetic Fortification**

The clinical interest in HMOs has increased with the development of synthetic and supplemented formulations. Available studies suggest that HMO-fortified nutrition can influence growth patterns, microbiota composition, and selected health outcomes in infants. In some trials, HMO supplementation has been associated with microbiota profiles that more closely resemble those observed in breastfed infants.

The clinical literature remains heterogeneous, however, and the strength of evidence varies by HMO structure, dose, population, and outcome measured. While early findings are encouraging, particularly for microbiota modulation and gut-related outcomes, more longitudinal studies are needed before firm conclusions can be drawn about broader clinical benefits.

### **Discussion**

The complex mechanistic pathways governed by these specific carbohydrates translate directly into significant protective clinical outcomes for vulnerable infant populations, demonstrating prophylactic capabilities against devastating neonatal diseases.

Necrotizing enterocolitis remains a catastrophic, frequently fatal inflammatory disease that rapidly destroys the delicate intestines of prematurely born infants. The fundamental pathogenesis is highly multifactorial, driven by profound mucosal immaturity, severe microbial dysbiosis, uncontrolled hyperinflammatory cascades, and rapid breakdown of the epithelial barrier (Prolacta Bioscience, 2024). Extensive basic science research and evolving clinical models demonstrate unequivocally that targeted glycan interventions provide critical protection against this lethal pathology. By operating as highly protective soluble decoys and actively promoting a fundamentally healthy microbial architecture, maternal glycans proactively prevent the initial dysbiosis that triggers the fatal disease cascade. Preclinical murine models emphatically demonstrate that targeted supplementation with specific synthetic analogs, such as two-prime-fucosyllactose, allows the fragile intestine to completely preserve its vital architectural integrity and to severely depress localized pro-inflammatory cytokine storms, even when deliberately challenged with lethal bacteria. Consequently, comprehensive meta-analyses indicate that an exclusive human milk diet is associated with a drastically lower overall risk of developing necrotizing enterocolitis in high-risk neonatal intensive care settings (Prolacta Bioscience, 2024).

Beyond immediate antimicrobial defense, early-life nutrition featuring these unique carbohydrates exerts sustained effects on permanent health outcomes by guiding fundamental epigenetic modifications (Jadavji & Krzeczowski, 2025). Through continuous microbial production of active metabolic byproducts, such as specific short-chain fatty acids, maternal glycans provide the biochemical substrates necessary to rapidly fuel complex epigenetic enzymes. Evidence suggests that short-chain fatty acids act as potent inhibitors of histone deacetylases, subsequently increasing cellular histone acetylation levels. Through these specific epigenetic modifications, the microbial metabolites directly regulate intestinal epithelial differentiation and immune cell function, contributing fundamentally to long-term immune tolerance and actively influencing the reduced development of allergic diseases (Wang et al., 2026).

Furthermore, the emerging scientific frontier in the study of maternal milk glycans involves their profound capacity to influence neurodevelopment through the bidirectional communication network known as

the gut-brain axis. The intensive metabolic activities of the specifically curated gut microbiota generate massive quantities of neuroactive biochemicals. Short-chain fatty acids, particularly butyrate, can directly cross the blood-brain barrier, thereby regulating regional brain energy metabolism and dampening localized neuroinflammation (Wichmann, 2024).

The rapid commercial integration of these newly synthesized molecules directly into consumer markets necessitates rigorous bioethical scrutiny regarding the fundamental design and subsequent interpretation of major pediatric nutritional clinical trials (Nelson, 2024). A persistent ethical controversy plagues comparative infant feeding research: the widespread practice of using standard, unfortified artificial formula as the primary baseline control group rather than universally using natural breastfeeding as the definitive physiological gold standard. Severe critics argue that this methodological approach fundamentally violates core rules of rigorous scientific research by treating an artificial physiological substitute as the normal biological baseline (Smith, 2023).

### Conclusions

The extensive body of contemporary scientific evidence undeniably establishes that complex maternal milk glycans are versatile biological orchestrators of the foundational infant gut microbiome and the rapidly developing neonatal immune system. By simultaneously fulfilling multiple distinct physiological roles - acting as specific prebiotics, potent soluble anti-adhesive decoys, advanced cellular immune modulators interacting with lectin and toll-like receptors, and vital epigenetic metabolic programmers - these molecules construct an impenetrable defensive shield that fundamentally determines long-term pediatric health.

Despite recent rapid progress, critical knowledge gaps persist. The precise molecular structure-function relationships of the vast majority of naturally occurring minor glycan variants remain to be elucidated. Future research trajectories must prioritize advanced, large-scale longitudinal clinical trials that leverage sophisticated multi-omics technologies to meticulously map the precise interactions among varying glycan blends, complex microbial cross-feeding networks, and precise systemic health outcomes. Addressing these distinct limitations will significantly refine personalized nutritional strategies, ultimately harnessing the profound evolutionary brilliance of natural human milk to optimize both immediate infant developmental trajectories and long-term adult metabolic resilience globally, ensuring optimal health outcomes across the entire human lifespan.

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