INTRODUCTION

In the early stages of life, microbes colonize the human body and live with the host for the rest of their lives. During crucial developmental windows, intestinal microbiota and its metabolites contribute to the programming of vital body systems like the immunological and central nervous system, potentially having long-term structural and functional effects. Injuries that can have long-lasting impacts on the microbiota-gut-brain axis can occur perinatally during these important developmental windows (during the first 1000 days). Environmental and parental factors, such as host genetics, mental health, nutrition, mode of delivery and feeding, exposure to antibiotics, immune activation, and antenatal microbiota composition, can all affect the microbiota composition of mother and child and may control key bodily functions.¹

Child health outcomes are related to the mother's nutrition during pregnancy and the baby's diet throughout infancy. The child's intestinal microbiome is the main source of postnatal immunological activation, which is linked to both health and disease in children. Nursing exclusively is advised for the first six months of a baby's life; otherwise, dairy-based infant formula is a supplement to breastfeeding. Numerous studies have shown that breastfed newborns have a different makeup of gut flora compared to infants fed formula. To highlight the important differences between human milk and infant formula in the development of the early intestinal microbiota and immune system, this study attempts to ignore any plausible explanations for some of the risks and benefits associated with human milk and infant formula. The approach was a literature review. A comprehensive search was done on the Pubmed Central® search engine. Using the Boolean operators "AND" and "OR," the search terms used are "breastfeeding," "formula," "microbiota," "intestinal," "human milk," and "infant." Among all the publications purchased, articles comprising various types of studies relevant to the literature review topic were picked. Breastfeeding is the preferred baby-feeding strategy. If exclusive breastfeeding is not preferred, infant formula prepared from cow's milk should be altered to promote the development of the infant's gut flora. Formulations could be modified by adding probiotic or prebiotic oligosaccharide agents.

Keywords: HMO, nutrition, prebiotic, probiotic.

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The impact of formula-fed feeding in comparison with breastfeeding to the infant’s intestinal microbiota: a literature review

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developing the early intestinal microbiota and immune system.

METHOD

A literature review served as the method. On the Pubmed Central search engine, a thorough search was conducted. The search terms utilized included "breastfeeding," "formula," "microbiota," "intestinal," "human milk," and "infant" using the Boolean operators "AND" and "OR." Articles containing various sorts of studies pertinent to the subject of the literature review were chosen from among all the articles acquired.

DISCUSSION

The infant's microbiota, composed of a wide variety of bacteria in different ecological niches along the intestine, develops at birth and is thought to be crucial for the infant's immediate health and the maturation of its intestinal system. Mammalian neonates are widely thought to be born with an intestine that is presumably sterile and are, therefore instantly exposed to various ingested germs, despite some claims that infants are especially exposed to bacteria before birth.

Breast Milk

The nutrition consumed during infancy may have a lasting impact on metabolism until adulthood. Although breast milk is the best infant nutrition, most infants also consume some formula. Despite obvious improvements, infant formulas can still reduce the gap between breastfed and formula-fed neonates. Improvements in metabolic health are highlighted, including decreasing the protein content, altering the lipid matrix, and adding prebiotics, probiotics, and synbiotics.\(^5\)

The gut microbiota's makeup may be impacted by feeding. Breastfed newborns are more likely to have Bifidobacteria and Clostridium difficile than formula-fed infants are to have Bacteroides and Clostridium perfringens. Penders et al. examined 100 full-term infants who were delivered vaginally and were not given any antibiotics. Breast-fed newborns showed reduced intestinal levels of E. coli (p=0.004) and Clostridium difficile (p=0.03) compared to formula-fed neonates.\(^6\)

The World Health Organization (WHO) advises nursing exclusively during the first six months of a baby's life. Breastmilk or newborn formula are not the exclusive sources of nutrition throughout any other stage of life, and the effects of early nutrition on health have been extensively discussed. For instance, breastfeeding is linked to lower long-term risks of atopy and obesity and lower risks of infection during infancy. Infant formula has enough macro- and micronutrients to suit the needs of a child growing quickly. However, numerous bioactive substances in human milk still have not been included in the formula. Several of these ingredients, including proteins and oligosaccharides, enter the large intestine partially undigested, impacting the formation of lower gut microbiota.\(^7\)

The preferred method of infant feeding is breastfeeding. Infant formula made from cow's milk should be modified to increase the growth of bifidobacteria if exclusive breastfeeding is not an option. This could be done, for instance, by adding probiotic or prebiotic oligosaccharide agents to formulas. However, most of the oligosaccharides now present in infant formula do not behave similarly to HMOs because of their structural differences. But now there are cow milk-based formulas containing 2'-FL or 2'-FL + LNnT additives that are chemically identical to breast milk ones.\(^8\)

Human milk oligosaccharides (HMOs), which are unconjugated lactose-based carbohydrate structures (74, 75), are the third most prevalent solid component in human milk after lactose and lipids with quantities between 7 and 14 g/L in mature milk and 20-24 g/L in colostrum. Recent research revealed the potential value of using HMOs in the newborn formula due to their involvement in boosting neonatal host defense mechanisms.\(^9\) Through various processes, breast milk bacteria have both short- and long-term roles in lowering the frequency and severity of bacterial illnesses in breastfed infants. Antimicrobial traits can be expressed or competitively excluded from harmful

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**Figure 1.** The microbiome of the mother's breast milk and the hypothesized process by which breast milk can change the microbiome of the infant's gut and affect their health. A mother's milk is customized for delivery to her child by various environmental, genetic, and immunological variables. Beginning with the first feeding, human milk oligosaccharides and breast milk bacteria contribute to the makeup and variety of the infant gut microbiome. The first gut bacteria may encourage the establishment of a normal or abnormal ecosystem. The community types may cause metabolic changes throughout the crucial period of immunological development, resulting in varying immune phenotypes and long-term health effects.
transformative changes because they lack defense mechanism genes, which could lead to pathogenicity and/or specific dysbiotic features like antibiotic resistance. These modifications may have an impact on the host's and the microbiota's capacity to maintain homeostasis through the induction of inflammation and other cellular stressors.

By replicating Human Milk's (HM) positive effects on the intestinal flora and the gut-associated immune system (GAIS), the new generation of newborn formulae tries to imitate HM. Several methods have been developed recently for creating new infant formulae (IF), including adding bioactive ingredients like probiotics, fructoligosaccharides (FOSs) and galactooligosaccharides (GOSs), human milk oligosaccharides (HMOs), and prebiotics, as well as obtaining what are known as post-biotics, also known as milk fermentation products.

**HUMAN BREAST MILK VS. INFANT FORMULA MILK**

Previous research on the gut microbiota variations between exclusively breastfed infants (EBF) and those who weren't has produced wildly varying results. In the first six months of life, non-EBF infants consistently have higher levels of gut bacterial diversity, microbiota age, relative abundances of Bacteroidetes and Firmicutes, and predicted microbial pathways related to carbohydrate metabolism than EBF infants, while relative abundances of pathways related to lipid metabolism, vitamin metabolism, and detoxification are lower. Infants born via Caesarean section experience greater variation in anticipated microbial pathways linked with non-EBF than infants born via vaginal delivery. Reduced diarrhea-related gut microbiota dysbiosis is connected with exclusive breastfeeding for longer. Additionally, after 6 months of age, EBF and non-EBF infants still have different gut flora.

A study conducted by Na Li et al. found that, compared to infant formula, human milk had a distinct effect on values for alanine transaminase, glutamic oxaloacetic transaminase, alkaline phosphatase, total protein, and triglycerides. Human milk also strengthened the immune system in...
comparison to infant formula, as shown by the analysis of blood cytokines (CD4+ lymphocytes, Th1, Th2, Th17, and Treg cells) and immunity markers (IL-2, IL-4, IL-9, and slgA). Comparing infant formula to human milk, the permeability of the intestinal mucosa was similarly reduced. Additionally, human milk enhanced the abundance of Akkermansia and Bacteroides, while infant formula boosted the quantity of Lactobacillus and Escherichia coli.16

According to the Chaos 1 index, there were no appreciable differences in the alpha diversity of the gut microbiota between the nursing and infant formula groups (p=0.346). Compared to the conventional formula group, the IF group's relative abundances of Enhydrobacter and Akkermansia were more comparable to those of the nursing group. The supplemented formula group and the breastfeeding group had comparable rates of ureolysis, according to the gut microbiota metabolism function prediction analysis (p=0.297). These results indicate that the overall bacterial diversity and some components of the fecal microbiota composition of formula-fed newborns would be similar to those of breastfed children.17

Overall, low microbial DNA amounts or sterility prevented the sequencing of some breast milk from healthy postpartum women. To further understand the causes of this phenomenon, research is required. The microbiota networks of babies that consumed bacterial milk were more complex and had higher Alpha diversity. These results offer a fresh understanding of milk microbiota and newborn gut microbiota.18

According to the review's overall body of research, POM feeding during the first few months of life maintains the makeup and colonization of the infant's gut microbiota in an appropriate way, which has effects on both the baby's immediate and long-term health. Additionally, POM (Parent's Own Milk) constituents mediate the interaction between the infant's gut microbiome and immune system activation, crucial for promoting tolerance, a healthy immune system's development, and preventing pathological imprinting. Numerous POM elements, including cells, bacteria, enzymes, and nutrients, are directly or indirectly involved in these important developmental processes.19

Commercial infant formula is neither a tailored nor dynamic form of nutrition because it lacks most of the immunomodulatory ingredients in POM. Even though donor human milk (DHM) preserves some of these components, processing stages change their bioactivity, and current DHM delivery methods are neither customized nor dynamic. Last, EPOM (Expressed Parent's Own Milk) feeding is the most similar substitute for DPOM (Direct Parent's Own Milk) and has several advantages. Still, it also changes the composition of the milk microbiota and hinders DPOM feeding's inherent dynamism and adaptability.19 The neonatal diet-associated metabolites may act as substrates and signals contributing to the physiological effects in HM and MF during infancy, with a fraction indicating diet-associated variations in microbial metabolism and ecology.20

In an epidemiological study of the early life microbiome, Coker MO et al. found that the delivery method has a lasting impact on the infant microbiota for up to one year. The microbiota development in premature infants is significantly impacted by breastfeeding and prolonged breast milk exposure, indicating a remedial effect of breast milk. These exposure-related differences represent significant areas that can be utilized for health-promoting therapies because the first few weeks and months of life are the most formative for immunological and microbiota development.21

In terms of richness and diversity, infants who consumed the infant formula compared to those who consumed the Standard formula had gut microbiota compositions that were more similar to those of breastfed infants and higher levels of calprotectin. Furthermore, we found that the infant formula and BF groups' main bacterial metabolic pathways were more comparable than those of the STD formula group. This suggests that using the innovative infant formula may change the gut microbiota composition, leading to a healthier intestinal microbiome.22

A follow-up study from Innova 2020 showed that after 12 months, the fecal microbiota, in silico metabolic pathways, and certain biochemical indicators associated with immunity were all affected similarly by the infant formula and the BF formula. A developing area of study that should always be assessed utilizing randomized clinical trials is the addition of novel substances to initial recipes. The mechanisms of microbial action by which the diet impacts the development of the gut during the first year of life and beyond should be the subject of future intervention research.23

Compared to the control formula, adding a combination of oligosaccharides obtained from cow's milk (BLOS) promotes gut maturation, bringing some of the markers studied here closer to those seen in infants who were nursed. A Randomized Controlled Trial found a significant relationship between changes in gut maturation markers like calprotectin and the microbiota. All of the formulas were well-tolerated and guaranteed the babies' secure development. This study's uniqueness involved tracking four gut maturation markers simultaneously in healthy-term newborns and speculating on how their infant formula intake would interact with early microbial colonization.24

The limitation of the studies mentioned above is the lack of deepening related to the side effects of breast milk or infant formula consumption. In addition to looking at the impact of milk consumption on intestinal microbiota activity, it is also necessary to pay attention to the impact in terms of maternal knowledge, infant tolerance to milk choices, economic impacts, and food input on mothers if they choose to breastfeed directly. In direct-breasted infants, the mother's nutritional status is an important factor to consider, and this has not been explicitly explained in previous studies. Hopefully, more research will discuss various other factors that can affect the state of the gut microbiota in infants so that the selection of milk feeding in infants can be appropriate.

CONCLUSION

Breastfeeding is the preferred baby-feeding strategy. If exclusive breastfeeding is not preferred, infant formula prepared from cow's milk should be altered to
promote the development of the infant's gut flora. For example, formulations could be modified by adding probiotic or prebiotic oligosaccharide agents. Infant formula feeding is a necessary option for various reasons, including difficulty in breastfeeding due to health concerns or economic factors (mother absent due to employment, single parents, etc.). However, infant formula feeding is not recommended until there are no other options, with breastfeeding being the preferred method and donor breast milk coming in second.

**CONFLICT OF INTEREST**

The author declares no conflict of interest.

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**AUTHOR CONTRIBUTION**

The author contributed to literature searching, data collecting, and manuscript preparation.

**REFERENCES**


