RESEARCH ARTICLE

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Gut Microbiota Modulation via Synbiotics: A Perspective for Boosting Antitumor Immunity and Inactivating Carcinogens in Early Life

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Abstract

Objective: Children are highly susceptible to infections and long-term health risks due to their immature immune systems, which typically develop fully around the age of 12. While early infections generate T and B memory cells, establishing a robust immune foundation is crucial not only for combating pathogens but also for preventing carcinogenesis in later life. Synbiotics, a synergistic combination of probiotics and prebiotics, offer a promising strategy to modulate the gastrointestinal microenvironment. **Method:** This article proposes that synbiotic supplementation provides dual benefits: enhancing immediate immunity and offering potential chemopreventive effects. **Result:** Mechanistically, synbiotics maintain microbial balance (increasing *Lactobacillus* and *Bifidobacterium*), which leads to (1) increased production of artificial endogenous immunoglobulins [Ma1.1][Ma1.2]like IgG to neutralize toxins and pathogens; (2) inactivation of cancer-causing chemicals and reduction of unwanted metabolite concentrations; and (3) enhancement of Natural Killer (NK) cell activity and antioxidant capacity, which are vital for tumor surveillance and reducing oxidative stress. By modulating the gut microbiota, synbiotics not only boost IgG levels to prevent common infections but also strengthen the body's defense against mutagenic agents. **Conclusion:** This opinion article summarizes clinical and preclinical findings to highlight the efficacy of synbiotics as a comprehensive immune booster and a potential agent for early cancer prevention strategies.

Keywords: Synbiotic- Probiotic- Cancer Prevention- Immune Booster- IgG levels- NK Cells

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Introduction

Establishing a robust immune foundation during childhood is a global health priority that extends beyond the immediate reduction of morbidity and mortality from infectious diseases [1]. In 2019, there were 5.3 million deaths of children under 5 years old, with 49.2% caused by infections such as pneumonia, diarrhea, and malaria [2]. Interventions and prevention measures typically involve maintaining cleanliness around the child's environment, but this is highly subjective and does not prevent infections overall. These children can still get infected if their immunity is low. Antibiotic therapy management for infectious diseases in children also does not have stable and consistent results due to the occurrence of multidrug-resistant (MDR) infections [3]. MDR incidence in neonates is 200,000 per year, where children have a high risk of MDR infection, 67.98% of which are gram-negative bacteria such as Escherichia coli, due to the inappropriate use of antibiotics by the mother and child [3, 4].

The pediatric immune system undergoes a prolonged maturation process, gradually reaching adult-like competence levels around the age of 12 [Ma2.1][Ma2.2] [5]. While infections occurring in these early years help build a repertoire of T and B memory cells to prevent reinfection [6], this "immune gap" period renders children highly susceptible not only to pathogens but potentially to the accumulation of cellular stress and early inflammatory processes. Physiologically, the gradual increase in serum immunoglobulin levels, such as IgG and IgA, reflects the maturation of the child's defense mechanisms against exposure [7]. This constant increase in IgG and IgA values indicates an increase in the number of pathogen exposures and the formation of the immune system in the child's body.

In clinical settings, artificial IgG is widely utilized for its anti-inflammatory and immunomodulatory effects

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to neutralize toxins and pathogens [Ma3.1][Ma3.2][8]. IgG antibodies function as neutralizers of toxins and pathogens by inducing phagocytosis and complement system activation. In a study of 394 pediatric pneumonia subjects, IgG and its subclasses' deficiency was found to be higher in this disease than in other immunoglobulins [9]. In addition, the use of IgG is also very efficient and has low side effects due to its high target cell specificity, making it suitable for use in children [8]. However, relying solely on reactive treatments is insufficient. Unlike artificial IgG, synbiotics aim to stimulate the host's endogenous production of immunoglobulins, offering a sustainable, long-term biological defense strategy that matures alongside the child. Emerging evidence suggests that early-life gut dysbiosis and chronic low-grade inflammation may serve as precursors to long-term health issues. Therefore, preventive strategies that modulate the internal environment to enhance immune surveillance the body's ability to detect and eliminate abnormal cells are crucial during this developmental window.

Synbiotics, a synergistic combination of probiotics (live microorganisms) and prebiotics (fermented substances), offer a promising approach to achieving this goal. They work by maintaining gastrointestinal microbial balance and physiologically activating gut microbiota metabolism [10]. Crucially, beyond their role in digestion, synbiotics possess significant chemopreventive potential; they have been shown to reduce concentrations of unwanted metabolites and, notably, inactivate cancer-causing substances [11]. By reducing the burden of carcinogenic metabolites and oxidative stress in the gut, synbiotics may play a pivotal role in preventing the initiation of cellular damage.

The administration of synbiotics, such as FLPP (a formula supplemented with native bovine lactoferrin (1 g/L) plus prebiotics (3' and 6'-sialyllactose oligosaccharides at a concentration of 6 g/L), was found to affect lower fecal calprotectin concentrations, which means that the incidence of intestinal inflammation is lower. In addition, the administration of *Lactobacillus* fermentum can also reduce gastrointestinal infections by 46% [12]. Another function of synbiotics is that in children with diarrhea, the administration of probiotics (*Lactobacillus* rhamnosus GG) can increase intestinal permeability and also increase IgG levels, but it is also stated that the mechanism behind this finding is still not fully understood [13]. Despite these benefits, current literature largely focuses on the efficacy of synbiotics for treating acute conditions, such as reducing the duration of diarrhea [15] or preventing gastrointestinal infections [12]. The potential of synbiotics to boost IgG levels explicitly for antitumor immunity potentially via mechanisms such as Antibody-Dependent Cellular Cytotoxicity (ADCC), where antibodies guide NK cells to target malignant cells and long-term chemoprevention in children remains under-discussed[Ma4.1][Ma4.2]. Consequently, this review aims to bridge this gap by summarizing clinical and preclinical findings on the efficacy of synbiotic supplementation. Specifically, we propose that synbiotics serve a dual function in early life: enhancing immediate immunity (IgG levels) and providing a long-term protective shield by inactivating carcinogens and modulating the gut microbiota against tumorigenesis.

What are Synbiotics?

Synbiotics are defined as a combination of probiotics and prebiotics that work synergistically to stimulate growth and/or activate the metabolism of gut microbiota physiologically [10]. The primary goal of this combination is to improve the survival of probiotic microorganisms in the digestive tract. By adding synbiotics to the diet, we not only enhance the food's nutritional value but also stimulate the proliferation of certain native bacterial strains found in the digestive tract. The most commonly used synbiotic combination involves the genus *Bifidobacterium* or *Lactobacillus* paired with fructooligosaccharides.

The action of synbiotics consists of two modes: increasing the viability of probiotic microorganisms and providing specific health effects. In the context of long-term health and chemoprevention, these effects are significant. Research has found that synbiotics increase the number of *Lactobacillus* and *Bifidobacterium* genera, maintain gut microbiota balance, and improve liver function a key organ for detoxification in patients with cirrhosis [11]. Most importantly for cancer prevention, synbiotics have been shown to reduce unwanted metabolite concentrations and inactivate cancer-causing substances (e.g., by reducing the activity of pro-carcinogenic enzymes like beta-glucuronidase or binding to mutagenic heterocyclic amines), as well as prevent bacterial translocation and increase immunomodulatory ability[Ma5.1][Ma5.2] [11].

Beyond detoxification, the use of synbiotics impacts metabolic factors that can influence tumorigenesis risk, such as glycemic control and lowering blood cholesterol levels [14]. They also function to balance gut flora to reduce the incidence of constipation and/or diarrhea, increase intestinal permeability, and directly stimulate the immune system [14].

In the pediatric population, establishing this microbial balance early is crucial. A meta-analysis by Yang et al. [15] showed that in children with acute diarrhea, synbiotics significantly decreased diarrhea duration, hospital stay, and bowel movement frequency compared to controls. In this study, synbiotics were found to have a more significant benefit than probiotics alone, as the prebiotic component increases the survival of probiotic compounds passing through the upper intestinal tract [15]. Furthermore, synbiotic formulations containing *Bifidobacterium* strains with galactooligosaccharides and fructooligosaccharides have provided benefits for optimal gut microbiota recovery in babies born via cesarean section [16]. This early restoration of gut homeostasis is a fundamental step in building a resilient immune system capable of handling carcinogenic threats in later life.

Synbiotics Supplementation: From IgG Enhancement to Antitumor Immunity

The human body operates as an intricate system requiring precise immunological surveillance to function optimally. Central to this defense mechanism is the gut microbiome. Recent studies have elucidated that the integrity of our gut microbiome significantly dictates our overall well-being, particularly the capacity of

the immune system to detect pathogens and aberrant cells [17]. Probiotics play a pivotal role in modulating this microbiome architecture. Unlike simple dietary adjustments, the strategic incorporation of probiotics serves as a foundational step for optimal health and long-term disease prevention. Understanding these benefits is crucial, not only for managing chronic illnesses but also for empowering the body's intrinsic surveillance systems against potential malignancies [17].

The gut microbiome exerts a profound influence on the maturation and function of the immune system, acting as a primary barrier against various infections and diseases, including tumorigenesis [18]. One established method to potentiate this system is through probiotic intervention. By modulating the gut ecology, probiotics stimulate the production of antibodies and activate specific immune cells capable of neutralizing threats. Crucially, they reduce the chronic low-grade inflammation that often precedes cancer development. Different genera, such as *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, possess distinct strains offering specific chemopreventive and immunomodulatory benefits[Ma6.1][Ma6.2]. This strain-specificity suggests that future synbiotic formulations for 'antitumor immunity' may need to be highly precise, aligning with the emerging concept of precision nutrition [19].

Boosting antitumor immunity via probiotics can be achieved through functional fermented foods like yogurt, kefir, and kimchi, which enhance microbiome diversity. Alternatively, dietary supplements offer a targeted approach, available in precise formulations [4]. Selecting the correct strain and dosage is essential for optimal immune support, especially when considering individual health status. Professional consultation is often necessary to tailor these interventions effectively [20].

Figure 1 summarizes the sophisticated interaction between intestinal microbiota and the immune system in maintaining homeostasis, a state vital for preventing the pro-inflammatory microenvironment that favors cancer initiation [21]. Microbiome-derived substances, such as TLR ligands and metabolites, modulate immunity locally and systemically. Cells like Foxp3+ Tregs and Th17 localized in Peyer's patches are critical; their balance regulates the production of secretory IgA (sIgA)[Ma7.1][Ma7.2]. Colonization by commensals like Bacteroides fragilis promotes regulatory T cells (Tregs), which dampen excessive inflammation. Maintaining this balance is crucial, as chronic, low-grade inflammation is often a recognized precursor to carcinogenesis in later life. Furthermore, early-life microbial colonization limits the expansion of invariant Natural Killer T cells (iNKT) cells that might otherwise exhibit disease-promoting activity in the lungs and lamina propria. Overall, maintaining this immune homeostasis is the first line of defense against cellular dysregulation.

This figure illustrates how microbiota-derived signals (e.g., metabolites, ligands) modulate immune responses in the gut mucosa. Synbiotics facilitate the colonization of beneficial commensals (e.g., *B. fragilis*, SFB (Segmented Filamentous Bacteria)) which promote the differentiation

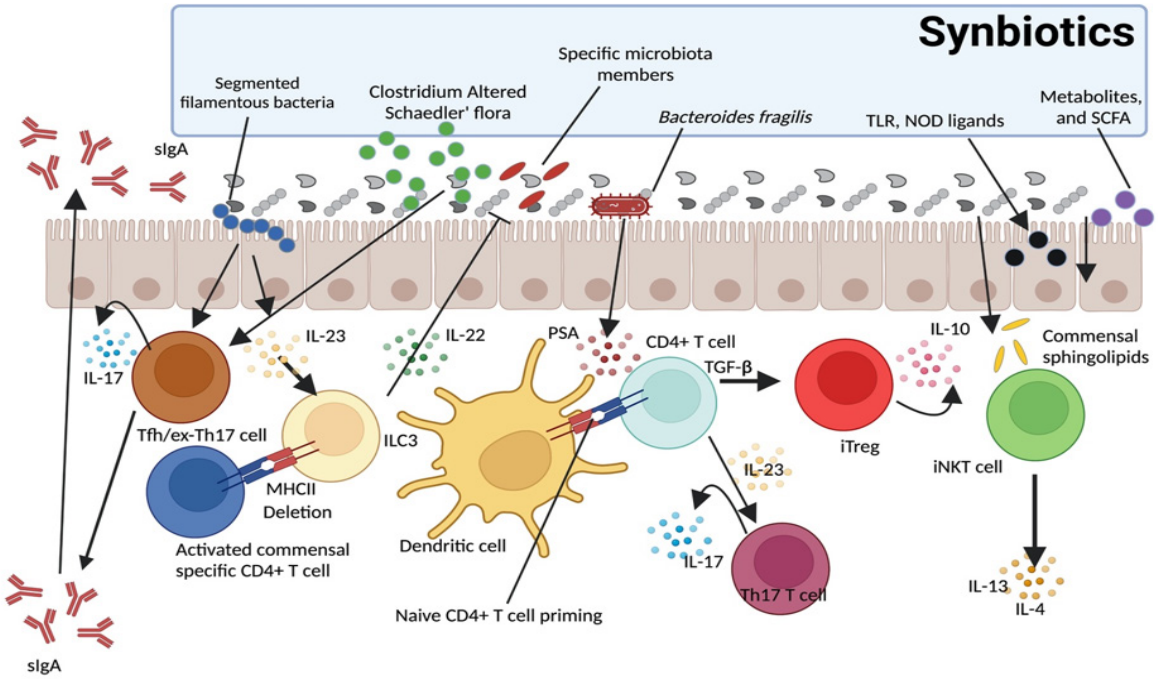

Figure 1. Mechanistic Interplay between Synbiotics, Gut Microbiota, and the Immune System in Maintaining Homeostasis and Preventing Pro-Inflammatory Dysbiosis. The figure illustrates how microbiota-derived signals modulate immune responses in the gut mucosa. Synbiotics facilitate the colonization of beneficial commensals (e.g., Bacteroides fragilis, Segmented Filamentous Bacteria) which release immunomodulatory molecules. Abbreviations: sIgA, Secretory Immunoglobulin A; SFB, Segmented Filamentous Bacteria; Tfh, T follicular helper cells; Th17, T helper 17 cells; MHCII, Major Histocompatibility Complex Class II; IL, Interleukin (e.g., IL-17, IL-22, IL-23, IL-10); ILC3, Group 3 Innate Lymphoid Cells; PSA, Polysaccharide A (immunomodulatory molecule from B. fragilis); TGF-β, Transforming Growth Factor-beta; iTreg, Induced Regulatory T cells; iNKT, Invariant Natural Killer T cells; TLR, Toll-like Receptor; NOD, Nucleotide-binding Oligomerization Domain; SCFA, Short-Chain Fatty Acids.

of regulatory T cells (Treg) and Th17 cells. Crucially for cancer prevention, this balance ensures robust immune surveillance while suppressing chronic inflammation and limiting the expansion of potentially disease-promoting cells like iNKT in the early stages of life.

The immunomodulatory reach of the microbiome extends beyond the gut, influencing organs such as the liver, brain, and lungs via the circulatory system (Figure 2) [21]. This "gut-organ axis" is critical for immunosurveillance. In the liver, while bacterial LPS can trigger inflammation, glycolipid antigen-containing probiotics have been shown to activate hepatic Natural Killer T (NKT) cells. These NKT cells are potent effectors in antitumor immunity, capable of destroying malignant cells. Similarly, microbiome-derived short-chain fatty acids (SCFAs) not only regulate microglial homeostasis in the CNS but also prime myeloid cells that migrate to the lungs to shape the pulmonary immune system. This systemic modulation highlights how gut-derived signals can bolster immune defenses in remote organs against carcinogenesis.

The immunomodulatory effects of synbiotics extend beyond the gut through the circulatory system. (Left) In the liver, probiotic components can activate Natural Killer T (NKT) cells, which are pivotal for antitumor immunity and clearing malignant cells. (Center & Right) Microbiome-derived short-chain fatty acids (SCFAs) regulate immune responses in the brain and prime myeloid cells in the lungs. This systemic modulation highlights the potential of synbiotics to strengthen defense mechanisms in remote organs against tumorigenesis.

To maximize these benefits, synbiotics combining probiotics and prebiotics are engineered to ensure probiotic survival and stimulate specific native bacterial strains [22]. Table 1 presents preclinical and clinical evidence of synbiotics, highlighting their role in enhancing specific immune components relevant to cancer prevention. Notably, studies in mini pigs (Row 3) demonstrate that synbiotics significantly increase antioxidant enzymes (CAT, GSH-Px, SOD) and reduce oxidative stress markers (MDA, H2O2), effectively acting as chemopreventive agents [25]. Furthermore, meta-analyses (Row 6) indicate that synbiotic mixtures can increase the activity of NK cells, which serve as the body's primary "search and destroy" mechanism for tumor cells [27].

Conclusions[Ma8.1][Ma8.2] and future direction of using synbiotics in children to boost their immunity

To sum up, synbiotics operate through two distinct yet complementary modes of action: increasing the survivability of probiotic bacteria during gastrointestinal transit and providing specific health benefits through metabolic modulation. Based on the summarized evidence, the utility of synbiotics extends far beyond the traditional scope of treating acute gastrointestinal infections. While the direct measurement of IgG levels in clinical settings remains a primary indicator of immune competence, this review highlights a broader potential: the role of synbiotics in chemoprevention and antitumor

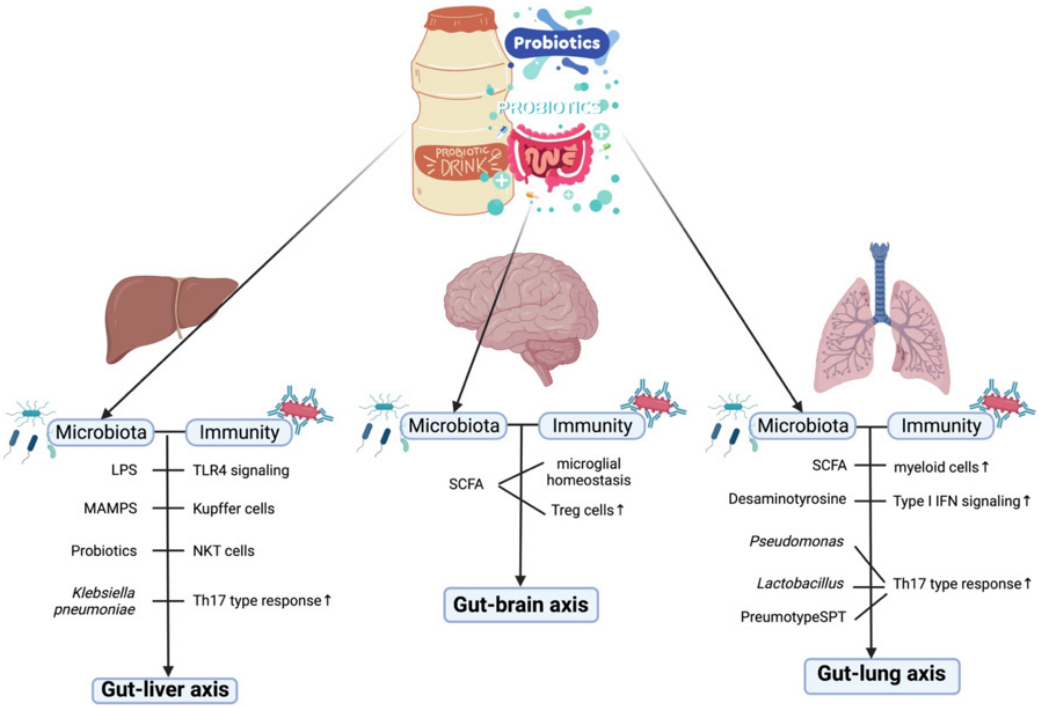

Figure 2. Synbiotic Supplementation Enhances Systemic Immunosurveillance and Antitumor Potential in Extra-Intestinal Organs via the Gut-Organ Axis. The diagram demonstrates how gut microbial metabolites and signals influence immunity in distant organs (liver, brain, lungs). Pathogens such as Klebsiella pneumoniae and Pseudomonas are depicted to illustrate how gut-derived immune signals (e.g., Th17 responses) enhance defense mechanisms against respiratory and hepatic infections. Abbreviations: LPS, Lipopolysaccharide; MAMPs, Microbe-Associated Molecular Patterns; TLR4, Toll-like Receptor 4; NKT, Natural Killer T cells; SCFA, Short-Chain Fatty Acids; Treg, Regulatory T cells; Th17, T helper 17 cells; IFN, Interferon.

Table 1. Summary of Preclinical and Clinical Studies Demonstrating the Immunomodulatory, Antioxidant, and Potential Chemopreventive Effects of Synbiotic Supplementation

References	Model	Types of synbiotics	Administration time	Main outcome
[15]	Meta-analysis of 34 studies on 4911 diarrhea patients	Strains of *Saccharomyces* and *Bifidobacterium* (compared against *Lactobacillus* mono-supplementation).	-	Strengthening of the intestinal barrier and modulation of cytokine profiles (increased TNF-α, decreased IL-4), resulting in reduced diarrhea duration and improved gut mucosal integrity.
[23]	Preclinical study – chicken	Inulin (1.76 mg), Bi2tos (0.528 mg), and *Lactobacillus* (1000 CFU).	3 weeks	Expansion of Bu1+ B-cell populations in the cecal tonsil, suggesting an enhanced potential for humoral immune responses and IgG production.
[24]	Preclinical study – Swiss albino mice	Fructooligosaccharide (FOS) (13 mg) combined with *Lactobacillus rhamnosus* GG (2×10^9 CFU).	During pregnancy and breastfeeding (7 weeks)	Significant enhancement of cellular immunity (phagocytosis and lymphocyte proliferation) and mucosal defenses. Demonstrated a 4-fold increase in specific antibody titers, indicating robust immune priming during early development.
[25]	Preclinical study – mini pig	Compound probiotic broth (*L. plantarum* $\geq 1.0 \times 10^8$ CFU/g and *S. cerevisiae* $\geq 0.2 \times 10^8$ CFU/g) supplemented with Xylooligosaccharides (XOS).	26 weeks	Modulation of gut microbiota favors beneficial genera (Firmicutes, Bifidobacterium). Crucially, synbiotics elevated antioxidant capacity (increased CAT, GSH-Px, SOD) and reduced oxidative stress markers (MDA, H2O2) in both colon and plasma, demonstrating systemic chemopreventive potential.
[26]	Clinical trial – adults	Multi-strain capsule containing *Bifidobacterium, Lactobacillus, Enterrococcus*, and *Bacillus* (0.5 g/capsule).	2 weeks during the COVID-19 infection	Elevation of total B lymphocyte counts, contributing to sustained humoral immunity during active infection.
[27]	Meta-analysis of 58 studies	Infant formula fortified with synbiotic mixtures.	-	Significant reduction in respiratory tract infection incidence accompanied by upregulated. Natural Killer (NK) cell activity, enhancing the body's innate surveillance system.

Note: Several outcomes highlighted in this table serve as key indicators for cancer prevention mechanisms. Specifically, the increase in antioxidant enzymes (CAT, SOD, GSH-Px) and reduction in oxidative stress markers (MDA, H_2O_2) [25], as well as the enhancement of Natural Killer (NK) cell activity [27], directly contribute to the body's chemopreventive capacity and antitumor surveillance.

surveillance during early life.

The in vivo and clinical evidence reviewed suggests that synbiotic supplementation creates a physiological environment hostile to carcinogenesis. Specifically, synbiotics have been shown to inactivate cancer-causing chemicals and reduce the concentration of unwanted metabolites. Furthermore, the modulation of the gut microbiota significantly increases antioxidant capacity by elevating levels of CAT, GSH-Px, and SOD while reducing oxidative stress markers like MDA and H_2O_2 [25] and enhances the activity of Natural Killer (NK) cells [27]. These mechanisms collectively strengthen the body's intrinsic ability to detect and eliminate cellular abnormalities before they progress to malignancy. Although direct correlation with specific tumor-antigen IgG levels requires further exploration, the observed increase in total B cell populations suggests a robust potential for humoral immunity improvement.

Moving forward, the paradigm of pediatric synbiotic research should shift from short-term infection control to long-term health programming[Ma9.1][Ma9.2]. Future clinical trials should not only measure standard immune markers (like total IgG or IgA) but also include biomarkers relevant to immunosurveillance and oxidative stress, such as NK cell cytotoxicity, specific tumor-associated antigen antibodies, and serum antioxidant levels. Specifically, long-term longitudinal cohort studies are essential to track this 'legacy effect' of early-life synbiotic supplementation on the incidence of chronic inflammatory diseases and malignancies in adulthood. Animal studies, particularly using mice models, should be designed to observe the direct effect of synbiotic supplementation on measuring

IgG responses to specific mutagenic challenges[Ma10.1] [Ma10.2], which may open a new horizon regarding the chemopreventive health benefits of synbiotics. Collectively, these findings support a dual-function model for pediatric synbiotic use: immediate infection control via enhanced IgG production and long-term chemoprevention through NK cell activation and oxidative stress reduction. By establishing a robust immune foundation early in life, synbiotics may serve as a crucial, low-cost strategy to reduce the lifelong burden of malignancy.

Author Contribution Statement

NCL and AFP: Contributed to the conceptualization and design of the critical opinion study. NCL, ASP, and ASNP: performed the literature search, formal analysis, and drafted the original manuscript. ASP and ASNP: Contributed to the visualization (Figures) and Table preparation. AFP: Contributed to the supervision, validation, and critical review and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

None.

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