

## LITERATURE REVIEW

English Version

OPEN ACCESS

# Crafting Paediatric Immunity: The Science of Prebiotic, Probiotic, and Synbiotic Roles in Child Health

## Membangun Kekebalan Tubuh: Pengetahuan tentang Peran Prebiotik dan Probiotik dalam Kesehatan Anak

Luciana Budiati Sutanto<sup>1</sup>, Charisma Dilantika<sup>2</sup>, Dessy Pratiwi<sup>3\*</sup>, Irma Rahayu Latarissa<sup>4</sup><sup>1</sup>Department of Nutrition, Faculty of Medicine, Krida Wacana Christian University, Jakarta, Indonesia<sup>2</sup>Health Collaborative Center, Jakarta, Indonesia<sup>3</sup>Indonesia Health Development Center, Jakarta, Indonesia<sup>4</sup>PT Dienggo Kreasi Nusantara, Jakarta, Indonesia

### ARTICLE INFO

Received: 20-12-2024

Accepted: 11-11-2025

Published online: 21-11-2025

**\*Correspondent:**

Dessy Pratiwi

[pratiwi.dessy@gmail.com](mailto:pratiwi.dessy@gmail.com)

DOI:

10.20473/amnt.v9i4.2025.747-766

**Available online at:**<https://e-journal.unair.ac.id/AMNT>**Keywords:**

Children, Immunity, Prebiotics, Probiotics, Synbiotics

### ABSTRACT

**Background:** The gut microbiota affects Children's immune system, which interacts with the immune system to support a healthy body. Prebiotics and probiotics, alongside their combination in the form of synbiotics, have demonstrated significant potential for enhancing immune health in children.

**Objectives:** This article aims to review the role of prebiotics, probiotics, and synbiotics in supporting pediatric immune health by discusses their mechanisms of action, clinical evidence of benefits, and their impact on infection risk reduction, gut health enhancement, and improved vaccine effectiveness.

**Methods:** A comprehensive literature review was conducted by utilizing recent studies and clinical trials on the effects of prebiotics, probiotics, and synbiotics on paediatric immune health.

**Discussions:** Prebiotics, probiotics, and synbiotics play a crucial role in supporting paediatric immune health by optimizing gut microbiota balance and facilitating the production of beneficial metabolites, such as short-chain fatty acids (SCFAs), which subsequently strengthen gut barrier function and modulate immune responses.

Prebiotics provide essential nutrients for beneficial bacteria, probiotics directly interact with immune cells, and synbiotics synergistically combine these benefits, demonstrating effectiveness in reducing infections, enhancing vaccine responses, and preventing allergies. Clinical studies highlight their potential to improve gastrointestinal health, reduce inflammation, and strengthen immunity, emphasizing their importance as safe and effective interventions for children's health.

**Conclusions:** Prebiotics, probiotics, and synbiotics demonstrate significant potential in supporting children's immune health through mechanisms that improve gut microbiota balance and enhance immune function. Despite encouraging findings, additional research is essential to determine optimal dosages, long-term safety, and individualized strategies for their clinical application.

### INTRODUCTION

Children's immune systems are instrumental in supporting their growth and development. A robust immune system could protect the body from various infections and ensure the body develops optimally<sup>1</sup>. In recent years, knowledge about the role of the gut microbiota in maintaining human health has grown rapidly. The gut microbiota, comprising billions of microorganisms, significantly influences a child's immune system. It not only provides protection against pathogens but also educates the immune system to respond to threats in an appropriate manner<sup>2</sup>.

Therefore, efforts to maintain children's immune health through gut microbiota management, such as the use of prebiotics and probiotics, are increasingly being

looked at as a promising solution<sup>3</sup>. While both have an important role in maintaining healthy gut microbiota, prebiotics and probiotics work in different ways. Prebiotics are non-digestible substances but provide a food source for good bacteria in the gut<sup>4</sup>. Meanwhile, probiotics are live microorganisms that provide health benefits when consumed sufficiently<sup>5</sup>. When prebiotics and probiotics are co-administered, they can synergistically promote gastrointestinal health and bolster the immune system<sup>6</sup>. The combination, known as synbiotics, has more significant potential to improve the balance of gut microbiota and boost overall immunity<sup>7</sup>.

Various studies conducted on children have shown that prebiotics and probiotics provide significant health benefits. Probiotics are effective in reducing the

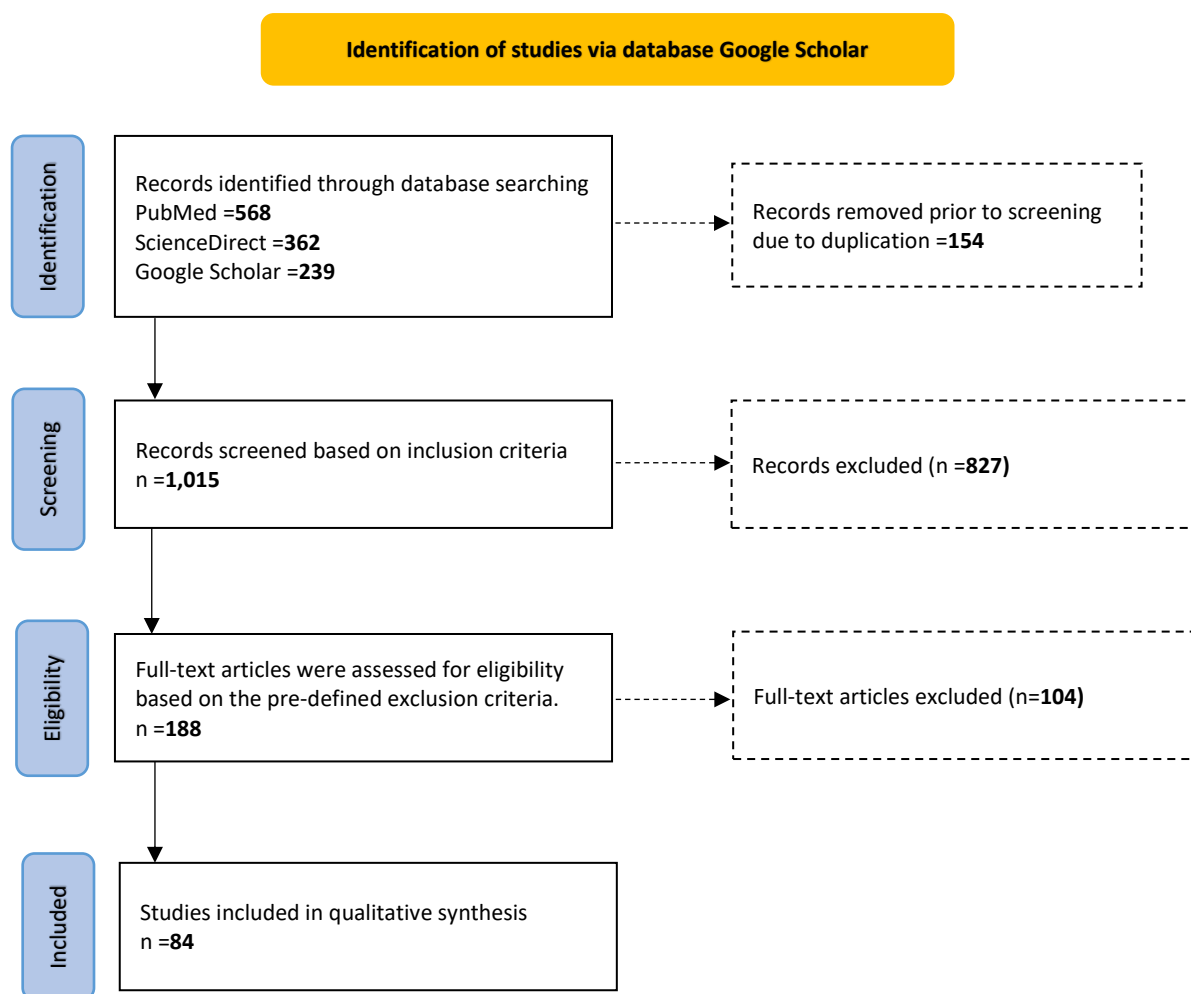
risk of gastrointestinal and respiratory infections and play a role in improving children's immune response to vaccines<sup>5</sup>. Prebiotics, on the other hand, strengthen the digestive system's health by increasing the production of Short-Chain Fatty Acids (SCFAs), which also play a role in reducing inflammation that can affect immune system performance<sup>4</sup>. Acting synergistically, these components create a favorable gut environment, thereby enhancing a child's resilience against infections and diseases.

While the benefits of using prebiotics, probiotics and synbiotics for children's health have been proven in numerous clinical studies, many challenges still need to be addressed in their development and implementation. Further research is urgently needed to determine the correct dosage and selection of appropriate probiotic strains and understanding the long-term effects of using these interventions on the immune system. In the future, a more personalized approach, based on individual microbiota profiles, could potentially provide a more effective solution in supporting children's immune health and disease prevention, taking into account each child's unique circumstances.

## METHODS

The method utilized in this article is a literature review, collecting and analysing recent research on the

roles of prebiotics, probiotics and synbiotics in child health. Data sources were identified through a structured search in scientific databases such as PubMed, ScienceDirect, and Google Scholar using keywords like "prebiotics," "probiotics," "synbiotics," "gut immunity," and "child health." Boolean operators (AND, OR) were applied to refine search results. The selected articles include experimental studies, clinical trials, reviews, systematic reviews and meta-analyses relevant to the mechanisms of action, clinical benefits, and immunological implications of prebiotics, probiotics and synbiotics. To ensure the relevance and quality of the included sources, the following inclusion criteria were applied: studies published within the last five years and those focused on the defined keywords. Exclusion criteria comprised grey literature, specifically unpublished theses, opinion articles, and non-peer-reviewed sources. A comparative analysis of the selected studies was conducted to highlight areas of agreement, divergence, and theoretical advancements. The synthesis aimed to provide a coherent narrative that contextualizes the existing body of knowledge and identifies potential avenues for future research. The collected data were synthesized to provide a comprehensive overview of the contributions of prebiotics, probiotics, and synbiotics in supporting paediatric immunity.



**Figure 1.** Flow diagram of study identification

## DISCUSSIONS

### The Gut-Immune Axis: Foundations of Paediatric Immunity

The gut, which hosts a highly diverse microbiome, serves as an “immune training ground” where the gut microbiota interacts directly with the immune system to shape and guide the development of the body's immune response. Crucially, these interactions are essential during childhood, as the immune system is still undergoing development<sup>8,9</sup>. The gut microbiota produces a variety of bioactive molecules, such as SCFAs, which play an important role in regulating inflammation and supporting the differentiation of immune cells, including regulatory T cells (Treg), which play a role in maintaining a balanced immune response<sup>10</sup>. Therefore, the gut not only functions as an organ of digestion but also as a vital control centre for developing the immune system in children<sup>11</sup>.

The concept of the gut-immune axis emphasizes the intrinsic link between the gut microbiota and optimal immune function in paediatric subjects<sup>12</sup>. The two-way communication pathway between the gut and the immune system allows the body to respond to pathogenic threats while tolerating non-pathogenic antigens such as food components or friendly microorganisms<sup>13</sup>. This process is crucial for maintaining balance in the immune system, which in turn plays a role in preventing overreactions to substances that should not harm the body. However, dysbiosis or microbiota imbalance may harm a child's immunity by increasing the risk of allergies, infections and inflammatory diseases<sup>14</sup>. Therefore, maintaining a diverse and balanced microbiota is crucial in supporting children's immune health, especially during their early years<sup>15</sup>. One effective way to achieve this is through a combined prebiotic and probiotic supplementation approach, which can optimize the gut microbiota composition. This supplementation fosters the proliferation of beneficial bacteria, augments the production of SCFAs, and modulates systemic inflammation, ultimately allowing paediatric immunity to function more effectively<sup>16</sup>.

### Gut as an Immunological Organ

The gut constitutes a central immunological hub in the human body, with over 70% of its immune cells dedicated to recognizing, tolerating, and combating various antigens<sup>17</sup>. In the gut microbiota environment, exposure to both commensal bacteria (good bacteria) and pathogens play a vital role in immune cells “education” process. Immune cells learn to distinguish between what should be tolerated, such as food and normal microbiota, and what should be attacked, i.e. pathogens or potentially damaging foreign bodies<sup>18</sup>. This process plays a vital role in building a tolerant immune system that can still respond appropriately to threats.

This interaction between the microbiota and the immune system supports the development of immune tolerance to non-pathogenic antigens while preparing the body's defences for harmful pathogens<sup>18</sup>. Through this training process, the gut helps balance an effective immune response and regulates excessive inflammation. This mechanism is crucial for preventing immune disorders, such as allergies and inflammatory diseases,

which can compromise pediatric health<sup>19</sup>. Thus, the gut microbiota plays a fundamental role in shaping and maintaining a healthy immune system, especially during childhood development.

The gut's ability to support immunological memory is critical to protecting the body from recurrent threats<sup>20</sup>. Early exposure to microbes, both commensal (beneficial) and pathogenic (harmful), plays a role in teaching the immune system to recognize specific patterns while strengthening adaptive responses to future exposure to similar microbes<sup>21–23</sup>. This immunological memory allows the body to respond faster and more effectively to similar infections in the future, reducing the risk of recurrent pathogen-induced disease<sup>24</sup>. In this context, maintaining a healthy gut microbiota through the support of prebiotics and probiotics, is a strategic step to improve immune function. This strategy not only demonstrates the potential to reduce infection risk but also contributes to the prevention of autoimmune and chronic inflammatory diseases that may arise from impaired immune balance in later life.

### Microbial Metabolites: a Key Link to Immune Health

SCFAs such as butyrate, acetate and propionate, produced by the gut microbiota, are important in regulating the body's immune response. These SCFAs not only strengthen the integrity of the intestinal barrier by improving epithelial layer function but also reduce intestinal permeability, which can lead to the leakage of toxins and microbes that trigger inflammatory responses<sup>25</sup>. By supporting anti-inflammatory pathways, SCFAs protect the body from systemic infections and maintain immune balance, crucial in preventing inflammation-related diseases.

In the context of paediatric health, the optimal production of short-chain fatty acids (SCFAs) by an eubiotic microbiota is a critical component in establishing a robust immune system. SCFAs also enhance the activity of immune cells such as regulatory T cells. These cells modulate immune responses to non-pathogenic antigens, such as food and normal gut microbiota<sup>26</sup>.

Moreover, SCFAs directly interact with the immune system through modulating the activity of immune cells such as macrophages, regulatory T cells, and dendritic cells. SCFAs can activate these cells to produce anti-inflammatory cytokines that suppress excess immune responses<sup>27,28</sup>. This is crucial for preventing chronic inflammation or autoimmune disorders resulting from immune system overreaction. In this way, short-chain fatty acids (SCFAs) counterbalance the body's reaction to threats, regulating immunity without causing damage due to excessive inflammation. Consequently, efforts to support SCFA production through prebiotic and probiotic intake are crucial for maintaining paediatric immune health<sup>29</sup>. Prebiotics, which serve as a food source for good bacteria, and probiotics, which increase the number of beneficial bacteria, both help to create an optimal microbiota environment<sup>30</sup>. This strategy not only supports the establishment of a balanced microbiota but also has the potential to prevent various inflammatory disorders and improve the ability of the child's body to fight infections,

thus contributing to a stronger and more disease-resistant immunity.

### Prebiotics: Nourishing Beneficial Microbes

Prebiotics, consisting of non-digestible fibres, play a crucial role in fostering the proliferation of beneficial gut bacteria, which influences immune function. Current research demonstrates that prebiotics contribute to the establishment of a eubiotic and balanced gut microbiota, thereby enhancing immune resistance in paediatric subjects. Prebiotics provide the necessary substrate for fermentation by the microbiota, producing essential metabolites such as SCFAs, which have anti-inflammatory effects and support balanced immune function<sup>31</sup>.

### Prebiotic Types and Sources

Prebiotics are a type of fibre that the body cannot digest but is important in supporting health. They serve as a food source for good microorganisms in the gut<sup>32</sup>. Some commonly recognized types of prebiotics include inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS). These compounds can be found in bananas, garlic and onions<sup>33</sup>. By their incorporation, prebiotics promote the proliferation of beneficial bacteria, such as *Bifidobacterium*, which is integral to maintaining an optimal immune system. Moreover, adequate intake of prebiotics also contributes to microbiota eubiosis, leading to enhanced systemic health overall<sup>34,35</sup>.

Bacteria such as *Bifidobacterium* play an essential role in regulating the immune system through tolerance mechanisms and protection against harmful microorganisms<sup>36</sup>. Prebiotics support this process by providing the nutrients required by good bacteria while helping to maintain the strength of the intestinal wall as the body's first layer of protection against pathogens<sup>37</sup>. Furthermore, prebiotics aid in modulating inflammation and enhance the immune response, which is particularly critical for children with developing immune systems<sup>38</sup>.

Incorporating prebiotic-rich foods into the daily diet represents a straightforward approach to promoting paediatric health<sup>39</sup>. While prebiotics could be obtained naturally from foods, further research is needed to determine the most effective dose and combination to support gut microbiota and immune system health. By understanding the sources and types of prebiotics, parents and health professionals can choose the right foods to support children's optimal growth and development.

### Mechanisms of Immune Enhancement

Prebiotics greatly benefit the immune system through their influence on the balance of gut microbiota and substances produced during digestion. One crucial mechanism involves promoting the production of short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate<sup>40</sup>. These compounds are formed when gut bacteria ferment prebiotic fibres. SCFAs play a role in strengthening the protective layer of the gut by increasing the production of proteins such as occludin and claudin, which serve to tighten the connections between cells in the gut wall<sup>41,42</sup>. This strengthening

prevents the translocation of pathogens and toxins into the bloodstream, thereby mitigating the risk of an excessive inflammatory response<sup>43</sup>. Furthermore, SCFAs also have anti-inflammatory properties that help suppress the production of inflammation-inducing cytokines such as interleukin-6 (IL-6) and Tumour Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and encourage the release of interleukin-10 (IL-10), which works to relieve inflammation<sup>44</sup>.

Furthermore, in terms of their effect on SCFA, prebiotics also play a role in stimulating the formation and increase of Treg. Through fermentation-derived metabolites, prebiotics assist Regulatory T cells (Treg cells) in curbing the overactivity of immune cells, specifically T helper 1 (Th1) and T helper 17 (Th17), whose unchecked function could precipitate inflammation or autoimmune diseases<sup>45,46</sup>. These Treg cells support immune system tolerance, crucial for preventing allergies and other immune disorders<sup>47</sup>. Not only that, prebiotics also encourage the growth of good bacteria such as *Bifidobacterium* and *Lactobacillus*. These bacteria produce bioactive substances that strengthen the protective layer of the gut and support immune cell function<sup>48</sup>. With these various ways of working, prebiotics are a crucial element in maintaining and improving immune system health, especially in children who are still growing.

### Clinical Evidence in Paediatric Health

Clinical research has shown that prebiotic supplementation can help reduce the risk of respiratory tract infections in children. A prospective randomized, double-blind, placebo-controlled study in healthy infants with a parental history of atopy found that supplementation of short-chain Galacto Oligo Saccharides (scGOS) and long-chain Fructo Oligosaccharides (lcFOS) significantly reduced the incidence of upper respiratory tract infections (p-value=0.07). In addition, the cumulative incidence of recurrent infections and recurrent respiratory infections in the scGOS/lcFOS group was also lower at 3.9% and 2.9%, respectively, compared to the placebo group at 13.5% and 9.6% (p-value<0.05)<sup>49</sup>. Similarly, a retrospective cohort study conducted in Indonesia involving children aged 18-38 months demonstrated that daily consumption of formula milk fortified with scGOS/lcFOS and n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFAs) for at least six months offered superior protection against Acute Respiratory Infections (ARI) in the preceding three months compared to the placebo group ((RR=0.62; 95% CI=0.41-0.92; p-value<0.05)<sup>50</sup>. This mechanism is believed to be related to the stimulation of immunoglobulin A (IgA) production in the gut, which is an essential component of the mucosal immune response against pathogens<sup>50</sup>.

In addition to their benefits in preventing infections, prebiotics have also been shown to improve gut health in children. Long-term studies show that prebiotic supplementation can increase *Bifidobacterium* and *Lactobacillus* populations, which play a role in suppressing the growth of pathogenic bacteria such as *Clostridium difficile*<sup>51</sup>. Another study evaluated the effects of GOS versus placebo in 20 children aged 4-16

years with chronic functional constipation through a placebo-controlled double-blind crossover study. The results showed significant changes, including increased bowel movement frequency ( $p$ -value $<0.001$ ), improved stool consistency ( $p$ -value $=0.014$ ), and reduced straining during bowel movements ( $p$ -value $<0.001$ )<sup>52</sup>. In addition, prebiotics are also known to strengthen the integrity of the intestinal epithelial barrier by increasing the production of tight junction proteins, thereby preventing conditions such as leaky gut that can trigger systemic inflammation<sup>53</sup>.

Moreover, to direct health benefits, prebiotics could also potentially improve vaccine efficacy. A study of influenza vaccine recipients reported that consumption of formula containing two different prebiotics (bifidogenic growth stimulator and galacto-oligosaccharides) and fermented milk products before immunization increased antibody titers against A/H1N1 for a more extended period than the control group. The number of *Bifidobacterium* was also significantly increased compared to the control group<sup>45</sup>. These findings emphasize that prebiotics not only support everyday health but also contribute to the success of childhood immunization programs.

#### Probiotics: Adding Beneficial Microorganisms

Probiotics, live microorganisms that provide health benefits when consumed sufficiently, are gaining increasing attention for their role in boosting the immune system. In paediatric health, probiotics play an important role by interacting directly with immune cells in the gut, such as macrophages, dendritic cells and T lymphocytes<sup>54</sup>. These interactions help regulate immune responses by increasing the production of anti-inflammatory cytokines, such as IL-10 while suppressing pro-inflammatory cytokines, such as TNF- $\alpha$ <sup>55,56</sup>. Some probiotic strains, such as *Lactobacillus rhamnosus* and *Bifidobacterium longum*, are also known to support the maturation of regulatory T cells, which prevent allergic reactions and autoimmune disorders in children<sup>57</sup>. With the ability to maintain a balanced gut microbiota and strengthen the body's protection against pathogens, probiotics are a potential option to support children's overall immune health.

#### Probiotic Mechanisms of Action

Probiotics work through complex and integrated mechanisms, interacting directly with intestinal epithelial cells and the immune system. One of the main mechanisms is to stimulate the production of IgA in the gut's mucosal lining<sup>58</sup>. IgA creates a natural barrier on the intestinal surface and prevents pathogens from attaching to the intestinal wall, reducing the risk of infection<sup>59–61</sup>. Probiotics also interact with dendritic cells the cells that link innate and adaptive immunity by enhancing their ability to detect pathogenic antigens and relay them to T lymphocytes<sup>5</sup>. This process produces a more targeted immune response without triggering excessive inflammation.

Strains such as *Lactobacillus rhamnosus* GG and *Bifidobacterium breve* are also known to strengthen the intestinal epithelial barrier by increasing the expression of intercellular binding proteins, such as claudin, occludin

and zonula occludens-1 (ZO-1)<sup>62,63</sup>. These proteins play an important role in maintaining the strength of the intestinal barrier, preventing leaky gut that can allow toxins or pathogenic microbes to enter the bloodstream<sup>64</sup>. Probiotics also regulate immune signalling pathways by suppressing the production of proinflammatory cytokines such as TNF- $\alpha$ , IL-6, and interleukin (IL-1 $\beta$ ) through inhibition of the Nuclear Factor Kappa-B (NF- $\kappa$ B) pathway<sup>65</sup>. Concurrently, probiotics stimulate the production of anti-inflammatory cytokines, notably IL-10, which contributes to the reduction of inflammation and the maintenance of immune tolerance<sup>66</sup>. Through these various mechanisms, probiotics help maintain immune balance, enhance the body's defence against pathogens, and prevent autoimmune disorders and allergies in children.

#### Evidence-Based Benefits in Paediatric Immunity

Clinical research has shown that probiotics could reduce the risk of gastrointestinal and respiratory infections in children. A systematic review and meta-analysis of 12 studies revealed that the administration of probiotics in treating acute diarrhoea in children could shorten the duration of diarrhoea, increase the effectiveness of therapy after two days, and shorten the period of hospitalization ( $p$ -value $<0.001$ )<sup>67</sup>. Another *systematic review* showed that probiotics could reduce the number of diagnosed ARI cases, decrease the incidence of ARI, shorten the average duration of acute ARI episodes, and reduce the use of antibiotics prescribed for acute ARI<sup>68</sup>. These results confirm that probiotics are important in strengthening the immune system while reducing the risk and impact of infectious diseases.

Certain strains, such as *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis*, have also shown promise in reducing allergic responses in children. A systematic review and meta-analysis of 11 clinical trials demonstrated that supplementation with *Lactobacillus rhamnosus* GG during pregnancy and lactation significantly reduced the risk of developing atopic dermatitis<sup>69</sup>. Another study by Enomoto et al. in 2014 reported that prenatal and postnatal supplementation with two species of *Bifidobacterium* may reduce the risk of eczema and atopic dermatitis in infants<sup>70</sup>.

However, this effect was not sustained once the infants surpassed ten months of age, emphasizing the critical role of the microbiota during the early stages of life in regulating allergic responses in paediatric subjects<sup>70</sup>. These results suggest that probiotics not only support immunity but can potentially prevent or reduce the severity of immunological disorders such as allergies in children.

#### Applications and Strain-Specific Effects

Various probiotic strains have unique specific benefits, which makes them usable according to clinical needs. For example, *Lactobacillus reuteri* is effective in reducing colic in infants, mainly by reducing excessive crying due to gastrointestinal distress. In addition, this strain is also associated with a reduced risk of gastrointestinal infections through its ability to inhibit pathogens and strengthen intestinal mucosal defences<sup>71</sup>. Meanwhile, *Bifidobacterium infantis* plays a vital role in

reducing gastrointestinal inflammation and improving the integrity of intestinal barrier function, which is an essential component in preventing systemic infections and other inflammatory disorders<sup>72</sup>.

Certain strain-based probiotics are often recommended by paediatricians to support immune function in a more targeted manner. *Lactobacillus reuteri*, for example, is recommended for infants at risk of colic disorders or gastrointestinal infections<sup>73</sup>, while *Bifidobacterium infantis* is more widely utilized in children with chronic inflammatory disorders or gut sensitivity issues<sup>74,75</sup>. This strain-based approach highlights the importance of understanding the different functions of each probiotic to ensure effectiveness in supporting children's health, both to prevent disease and facilitate optimal recovery.

### Synbiotics: The Synergy of Prebiotics and Probiotics

Synbiotics are a combination of prebiotics and probiotics that improve the body's health, especially by supporting immunity. Prebiotics serve as a source of nutrients that promote the growth of probiotics in the gut while probiotics utilize prebiotics to produce SCFAs and other metabolites that benefit the immune system<sup>76</sup>. This collaboration creates a more substantial synergistic effect than using the two separately. Synbiotics help maintain a balanced microbiome, strengthen the gut barrier and reduce inflammation, creating a stable and healthy gut environment. With these benefits, synbiotics effectively support children's immune systems and maintain long-term health<sup>77</sup>.

### Mechanisms of Synbiotic Action

Synbiotics work by enhancing probiotic colonization by providing a supportive environment for beneficial bacteria through prebiotics<sup>37</sup>. Prebiotics such as inulin, FOS and GOS act as substrates that feed probiotics such as *Lactobacillus* and *Bifidobacterium*. The presence of these prebiotics accelerates the growth and proliferation of probiotic bacteria in the gut, improving the balance of the gut microbiota<sup>78</sup>. The increased number of probiotics in the gut leads to increased production of SCFAs such as acetate, propionate and butyrate<sup>79</sup>. These SCFAs have several significant benefits, including maintaining the integrity of the gut wall, reducing inflammation, and improving gut barrier function that can prevent pathogens and toxins from entering the body<sup>80</sup>.

In addition, SCFAs produced by probiotic microbiota also have a significant immunomodulatory impact. SCFAs promote the differentiation and activation of Tregs, which play an important role in controlling immune responses and preventing allergic reactions and autoimmunity<sup>25</sup>. SCFAs also stimulate immune cells in the epithelial lining of the gut to produce more potent antimicrobial molecules, enhancing local defence against infection<sup>81</sup>. By improving gut barrier function, synbiotics reduce gut permeability and enhance the systemic immune response, providing additional protection against systemic infections. Synbiotics, in this way, increase the body's capacity to respond effectively to pathogens, reduce inflammation, and strengthen overall

immunity, which is crucial in developing a child's immune system<sup>16,76,82</sup>.

### Clinical Evidence of Synbiotic Benefits

Clinical research reveals that synbiotics can help shorten the duration of infection in children while reducing antibiotic overuse. A systematic review and meta-analysis showed that interventions using synbiotics and probiotics significantly shortened the duration of diarrhoea and hospitalization, decreased the frequency of bowel movements on day 3, and reduced the incidence of diarrhoea lasting more than 3 days compared to the control group. In addition, subgroup analysis showed that synbiotics were more effective than probiotics in reducing diarrhoea duration and hospitalization<sup>83</sup>. In addition, the study documented a reduction in the use of antibiotics among children who consumed synbiotics, particularly those used to treat infections associated with diarrhoea. This finding suggests that synbiotics can accelerate the recovery process and mitigate reliance on antibiotics, which, in turn, can curb the development of antibiotic resistance<sup>84</sup>.

Synbiotics are also beneficial in lowering the risk of allergic diseases in children. A clinical trial showed that children who received  $\alpha$ -lactalbumin-enriched supplementation with synbiotics had a lower risk of developing atopic dermatitis than the control group (2.6% vs. 17.8%, p-value<0.05)<sup>85</sup>. This reduction was attributed to the improved balance of the gut microbiota and a strengthened immune response that helps regulate inflammation. In addition, a separate study showed that synbiotic administration significantly ameliorated symptoms such as recurrent wheezing and noisy respiration that were not attributable to colds in children. The number of children who initiated asthma medications during the study was also significantly lower in the synbiotic group than in the placebo group<sup>86</sup>. This finding confirms the role of synbiotics in supporting children's immune response to allergens while helping to prevent and reduce the severity of allergic disorders.

Overall, this clinical evidence suggests that synbiotics not only improve gastrointestinal health but also play an essential role in strengthening the immune system and protecting children from allergic diseases. Combining prebiotics and probiotics in synbiotics provides greater synergistic benefits in overall immune support, making it a valuable intervention to support immunological health during childhood<sup>76</sup>. The improved microbiota balance produced by synbiotics also has the potential to be an effective preventive measure in preventing various inflammatory and allergic diseases in the future.

### Safety and Considerations in Paediatric Use

In the administration of prebiotics, probiotics, or synbiotics in paediatric patients, proper dosage, strain selection, and individual factors should be primary considerations to ensure maximal benefits and preclude adverse effects. Prebiotics and probiotics should be tailored to the child's age, health condition, and individual response to the therapy. For example, too high a dose of probiotics may cause gastrointestinal distress or other side effects, while an inappropriate strain may have

a less effective impact on the immune system<sup>87</sup>. Therefore, it is essential to consult with medical personnel to select an appropriate strain, such as *Lactobacillus rhamnosus* GG to boost the immune system or *Bifidobacterium infantis* to support gut health. Although generally safe, the administration of synbiotics in children with pre-existing medical conditions, specifically immune system disorders or chronic diseases, warrants caution and must be conducted under professional medical supervision<sup>88</sup>. Proper guidance and safe use practices can help maximize the health benefits of prebiotics, probiotics and synbiotics for children.

### Dosage and Age-Appropriate Use

The dosage of prebiotics and probiotics in children should be adjusted according to each child's age, weight, and health condition. This dosage adjustment is essential to achieve the therapeutic benefits safely and effectively. For example, children with lower body weights or younger ages may require smaller doses than older or older children. In addition, children who have digestive problems or certain health disorders may need more attention in terms of dose selection and the type of strain used<sup>89</sup>. Research by Huang et al. in 2021 showed that the use of probiotics in children at the right dosage could help reduce the duration of infectious diarrhoea without causing adverse side effects<sup>67</sup>.

Furthermore, it is recommended to introduce prebiotics and probiotics gradually, especially in children who are taking them for the first time, as some children may experience mild gastrointestinal symptoms, such as bloating or stomach discomfort, at the beginning of their use. For example, a study published by Garcia et al. (2023) showed that children given probiotics gradually experienced decreased gastrointestinal side effects, with better tolerance to the therapy<sup>90</sup>. This emphasizes the importance of starting administration at a low dose and slowly increasing the dose over time to maximize therapeutic benefits while reducing potential side effects.

### Safety Profiles and Contraindications

Generally, prebiotics and probiotics are considered safe for children, but they have rare side effects, such as bloating or stomach discomfort. These side effects are usually mild and temporary, often occurring early in use as the body adapts to the changes in gut microbiota. In some studies, a small percentage of children taking probiotics report mild symptoms such as bloating or gas. Still, these side effects tend to disappear after a few days<sup>88,91</sup>. Nonetheless, these side effects need to be monitored, and the correct dosage should be adjusted according to each child's condition to minimize discomfort.

However, the use of prebiotics and probiotics in children with pre-existing health conditions, particularly those with compromised immune systems (e.g., immunocompromised patients or those on immunosuppressive therapy), requires prudence. In children with compromised immune status, probiotic administration may elevate the risk of systemic infections, such as sepsis, attributable to certain strains of probiotic bacteria. One study reported a few cases of

severe infections in immunocompromised children taking probiotics, although the incidence was rare<sup>92</sup>. Therefore, it is very important to consult a doctor or paediatrician before starting prebiotic or probiotic therapy, especially for children who have medical conditions that may affect their immune systems.

### Future Directions in Prebiotic, Probiotic, and Synbiotic Research

Although the current findings show promising results, further research into the long-term impact, personalized approach and optimal dosage for various paediatric populations remains ongoing. Future research should focus on developing a deeper understanding of strain-specific effects and how gut microbiota may play a role in preventing chronic conditions, such as allergic diseases, obesity and metabolic disorders. Research should also look at the interactions between prebiotics, probiotics and synbiotics, as well as genetic factors and environmental conditions that influence the development of a child's immune system. Thus, more detailed studies will provide more comprehensive insights to improve microbiota-based therapies in supporting paediatric health more effectively and purposefully.

### Personalised Microbiota Interventions

Given technological advances in gut microbiota analysis, a personalized approach tailored to each paediatric patient's microbial profile can yield superior immune support<sup>93</sup>. Every child has a different microbiota, and understanding that microbiota can help determine which prebiotics and probiotics work best for them. For example, if a child exhibits a low abundance of beneficial bacteria, such as *Bifidobacterium*, providing the appropriate prebiotics can promote their proliferation, consequently enhancing their gastrointestinal and immune health<sup>94</sup>.

This approach can help minimize unwanted side effects and ensure more optimal results. We can provide more appropriate therapy for each child by considering age, weight, health conditions and other factors<sup>89</sup>. While more research is still needed, this customized approach has great potential in supporting children's health, especially in strengthening the immune system and preventing disease.

### Potential for Disease Prevention and Immune Training

Future research needs to explore how early intervention with prebiotics and probiotics can shape immune memory in children. Good immune memory in childhood could provide long-term protection against chronic diseases and autoimmune conditions later in life<sup>95</sup>. By modulating immune responses early on, we can optimize children's immunity to recognize and fight pathogens more efficiently and reduce the risk of future immune disorders. Several studies have shown that intervening with probiotics from an early age may increase the body's resistance to infection, which in turn helps reduce the development of long-term diseases<sup>96</sup>.

In addition, research also needs to examine further how prebiotics and probiotics play a role in training the immune system to respond appropriately to

pathogens, prevent excessive inflammation, and avoid developing autoimmune diseases. By providing appropriate interventions in the early stages of life, prebiotics and probiotics can help children develop a more balanced and robust immune system, which can last well into adulthood. This approach offers great potential to reduce the prevalence of immune-related diseases and improve quality of life in the future.

#### **Strengths and Limitations of the Study**

This review provides a comprehensive overview of how prebiotics, probiotics, and synbiotics support paediatric immune health, based on recent research findings. Its key strength lies in integrating biological mechanisms with clinical findings to present a complete picture. However, it relies on existing studies and lacks original clinical data, which limits conclusions about dosage, safety, and personalised use.

**Table 1.** Summary of Study Included in the Analysis

| Authors (Year)            | Objectives                                                                          | Study Design       | Methods                                                     | Key Results                                                                                                                                |
|---------------------------|-------------------------------------------------------------------------------------|--------------------|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Li et al. (2023)          | Evaluate effects of synbiotics on immune markers & gut microbiota in healthy adults | Double-blind RCT   | Synbiotic vs placebo; immune profiling; 16S rRNA sequencing | Synbiotics significantly enhanced beneficial taxa, increased anti-inflammatory cytokines, and improved microbiota diversity.               |
| Okolie et al. (2024)      | Summarize links between gut microbiota and immunity                                 | Narrative review   | Literature synthesis                                        | Demonstrates that microbiota regulates innate/adaptive immunity, with dysbiosis linked to chronic inflammation and disease susceptibility. |
| Mpakosi et al. (2025)     | Examine role of infant gut virome in immunity & autoimmunity                        | Narrative review   | Viral–microbiota–immune literature                          | Early virome composition shapes immune maturation; disruptions associated with autoimmunity risk.                                          |
| Duan et al. (2023)        | Assess SCFA effects on macrophage activity                                          | Mechanistic review | Cellular, molecular, immunological evidence synthesis       | SCFAs modulate macrophage polarization, suppress inflammatory signaling, and show therapeutic potential in chronic inflammatory diseases.  |
| Dera et al. (2025)        | Explore microbiota’s impact on immune development & allergies                       | Review             | Evidence synthesis                                          | Early-life microbial exposure modulates Th1/Th2 balance; dysbiosis increases allergic sensitization risk.                                  |
| Yuan et al. (2023)        | Review gut–brain axis and innate immunity in infections/inflammation                | Review             | Cross-sectional scientific synthesis                        | Microbiota influences neuroimmune pathways; dysbiosis contributes to neuroinflammation and infectious susceptibility.                      |
| Kasarello et al. (2023)   | Describe immune & neuroendocrine communication in gut–brain axis                    | Review             | Mechanistic evidence synthesis                              | Shows bidirectional microbiota–brain signaling through cytokines, vagal pathways, and endocrine mediators.                                 |
| Pantazi et al. (2023)     | Evaluate gut microbiota–allergy relationships in children                           | Literature review  | Pediatric data review                                       | Reduced early microbial diversity and specific taxa loss linked to asthma, eczema, and food allergies.                                     |
| Yao et al. (2021)         | Review microbiota’s role across lifespan                                            | Review             | Multi-stage microbial development analysis                  | Highlights critical windows in infancy shaping immunity, metabolism, infection risk, and long-term health.                                 |
| Kim & Mills (2024)        | Review probiotics, prebiotics, synbiotics & postbiotics                             | Review             | Synthesis of clinical and mechanistic findings              | Demonstrates beneficial modulation of immune pathways, inflammatory mediators, and gut barrier integrity.                                  |
| Wiertsema et al. (2021)   | Summarize microbiome–immune interactions across life                                | Review             | Infectious disease focus synthesis                          | Microbiota influences infection outcomes via immune priming; nutrition and microbial therapies can enhance host defense.                   |
| Zheng et al. (2020)       | Review microbiota–immunity crosstalk                                                | Mechanistic review | Multi-omics & immunology synthesis                          | Identifies pathways linking dysbiosis to autoimmunity, metabolic disease, and chronic inflammation.                                        |
| Heravi (2024)             | Explore microbiota–autoimmune disease links                                         | Review             | Mechanistic & therapeutic evidence synthesis                | Dysbiosis contributes to aberrant immune activation; microbiome-targeted therapies show emerging benefit.                                  |
| Zhang et al. (2025)       | Explain gut–brain–immunity links in cognitive decline                               | Review             | Neuroimmune literature synthesis                            | Dysbiosis promotes neuroinflammation and cognitive impairment via microbial metabolites & immune signaling.                                |
| Al Nabhani & Eberl (2020) | Investigate early-life microbiota immune imprinting                                 | Review             | Synthesis of developmental immunology                       | Early microbial exposure shapes immune tolerance; disruptions increase chronic inflammation risk.                                          |

| Authors (Year)           | Objectives                                                      | Study Design              | Methods                                                           | Key Results                                                                                                                             |
|--------------------------|-----------------------------------------------------------------|---------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Fadlyana et al. (2022)   | Assess air pollution's impact on child gut microbiota           | Expert consensus          | Evidence appraisal                                                | Air pollution consistently disrupts gut microbial composition, increasing risk of allergies & metabolic dysfunction.                    |
| Endaryanto et al. (2023) | Characterize air pollution–allergy–infection triad              | Expert review             | Synthesis of mechanistic & epidemiologic sources                  | Pollution worsens respiratory disease via dysbiosis, impaired mucosal immunity, and increased infection susceptibility.                 |
| Bugya et al. (2021)      | Describe levels of immunological memory & relevance to vaccines | Review                    | Immunological synthesis                                           | Identifies multiple memory layers (innate, trained, adaptive) relevant for vaccine optimization.                                        |
| Ney et al. (2023)        | Examine SCFAs in local/systemic inflammation                    | Review                    | Molecular immunology synthesis                                    | SCFAs regulate cytokine production, T-cell differentiation, and epithelial barrier function.                                            |
| McBride et al. (2023)    | Test SCFA-mediated epigenetic modulation of T cells             | In-vitro experimental     | Culture of inflammatory T cells; SCFA exposure; epigenetic assays | SCFAs induced histone acetylation and suppressed pro-inflammatory gene expression in T cells.                                           |
| Liu et al. (2023)        | Summarize SCFA regulation of immunity                           | Review                    | Mechanistic & clinical data synthesis                             | SCFAs modulate innate and adaptive immunity, promoting tolerogenic responses and limiting inflammation.                                 |
| Liu et al. (2024)        | Evaluate SCFA effects on intestinal mucosal immunity in pigs    | Review                    | Animal nutritional immunology synthesis                           | SCFAs improve epithelial integrity, mucosal immunity, and resistance to intestinal pathogens.                                           |
| Hsu et al. (2024)        | Review SCFAs in pediatric health                                | Review                    | Synthesis of developmental & neuroimmune evidence                 | SCFAs regulate gut maturation, neuroprotection, and inflammation; deficiency linked to pediatric disorders.                             |
| Ji et al. (2023)         | Review probiotics, prebiotics & postbiotics                     | Review                    | Synthesis of clinical & mechanistic integration                   | All biotic classes influence immune homeostasis and barrier function; postbiotics show promising translational value.                   |
| Holmes et al. (2022)     | Assess microbiota response to different prebiotics              | Human intervention        | Prebiotics administration; microbiome sequencing                  | Prebiotic responses showed strong intra-individual consistency; habitual fiber intake predicted microbial shifts.                       |
| Bevilacqua et al. (2024) | Update on prebiotics & health                                   | Review                    | Human & animal data synthesis                                     | Prebiotics consistently improved microbiota composition, immune markers, and metabolic health.                                          |
| Kaewarsar et al. (2023)  | Optimize inulin+FOS+GOS mixtures for probiotic stimulation      | Experimental optimization | Prebiotic mixture modeling; probiotic growth assays               | Mixed prebiotics synergistically enhanced probiotic growth and metabolic activity.                                                      |
| Yoo et al. (2024)        | Explain prebiotics' role in microbiota modulation               | Review                    | Molecular & clinical evidence                                     | Prebiotics support beneficial taxa, improve SCFA production, and modulate inflammatory pathways.                                        |
| Pujari & Banerjee (2021) | Examine prebiotics' immune effects                              | Review                    | Bench-to-clinic synthesis                                         | Prebiotics enhanced mucosal immunity, regulatory T-cell activity, and vaccine responsiveness.                                           |
| Gavzy et al. (2023)      | Investigate Bifidobacterium mechanisms in immune tolerance      | Review                    | Immunological and microbial analysis                              | Bifidobacteria promote immune tolerance via SCFA production, dendritic cell modulation, and Treg induction.                             |
| Simon et al. (2021)      | Examine roles of probiotics, prebiotics, synbiotics in IBS      | Narrative review          | Synthesis of clinical and mechanistic evidence                    | These interventions modulate gut microbiota, reduce inflammation, improve gut barrier function, and alleviate IBS symptoms.             |
| Pujari & Banerjee (2021) | Assess prebiotics' impact on immune responses                   | Review                    | Evaluation of prebiotic–immune interaction studies                | Prebiotics enhance innate and adaptive immunity via SCFA-mediated pathways, improving host defense and reducing inflammatory responses. |

| Authors (Year)            | Objectives                                                                      | Study Design                        | Methods                                                                 | Key Results                                                                                                                         |
|---------------------------|---------------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Selvamani et al. (2023)   | Review effects of prebiotics in newborn and child health                        | Review                              | Analysis of pediatric prebiotic interventions                           | Prebiotics improve gut maturation, immune development, reduce infections, and support metabolic homeostasis in children.            |
| Mirzaei et al. (2021)     | Summarize roles of microbiota-derived SCFAs in neurological disorders           | Review                              | Integration of microbiome–brain axis evidence                           | SCFAs influence neuroinflammation, blood–brain barrier integrity, and neurodegenerative disease progression.                        |
| Ma et al. (2022)          | Explore interactions among gut microbes, intestinal barrier, SCFAs              | Review                              | Molecular and physiological evidence synthesis                          | SCFAs maintain epithelial barrier integrity, modulate immunity, and prevent dysbiosis-related disorders.                            |
| Facchin et al. (2024)     | Summarize metabolic pathways and therapeutic uses of SCFAs                      | Review                              | Examination of SCFA biosynthesis and clinical data                      | SCFAs show therapeutic potential in metabolic disease, inflammation, and gut barrier repair.                                        |
| Fusco et al. (2023)       | Identify key SCFA-producing bacterial taxa                                      | Review                              | Microbiome taxonomic and functional review                              | SCFA-producers (e.g., <i>Faecalibacterium</i> , <i>Roseburia</i> ) are central to gut homeostasis and reduced in multiple diseases. |
| Du et al. (2024)          | Clarify roles of SCFAs in inflammation and health                               | Review                              | Compilation of immunological and metabolic studies synthesis            | SCFAs reduce systemic inflammation through GPCR activation, epigenetic regulation, and cytokine modulation.                         |
| Zhou et al. (2024)        | Examine combined therapeutic roles of pro-, pre-, and postbiotics               | Review                              | Synthesis of clinical/molecular findings                                | Synergistic modulation of gut immunity, barrier integrity, and microbiome composition is observed.                                  |
| Liu et al. (2022)         | Assess microbiota and immunity modulation by biotics                            | Review                              | Overview of probiotic/pre/postbiotic mechanisms synthesis               | Biotics regulate cytokines, improve barrier function, and rebalance dysbiosis-linked inflammation.                                  |
| Goswami et al. (2022)     | Review therapeutic potential of Tregs in autoimmune diseases                    | Review                              | Immunological and therapeutic literature analysis                       | Tregs restore tolerance and reduce autoimmune inflammation, but clinical translation remains challenging.                           |
| Pedrosa et al. (2024)     | Link prebiotic structural diversity to immune and barrier outcomes              | Review                              | literature analysis of structural–functional mapping of prebiotic types | Distinct prebiotic structures selectively promote beneficial taxa, enhance barrier integrity, and modulate immune tolerance.        |
| Gulliver et al. (2022)    | Describe future microbiome-based therapeutics                                   | Review                              | Literature analysis of microbial therapeutics, FMT, next-gen probiotics | Personalized microbiome therapeutics likely to expand; precision design improves efficacy over empirical approaches.                |
| Dewi et al. (2024)        | Determine effects of fortified milk on URTI risk in Indonesian children         | Retrospective cohort                | Medical records review                                                  | Regular fortified milk consumption significantly reduced URTI incidence.                                                            |
| Dou et al. (2022)         | Evaluate effects of FOS on human gut microbiota                                 | Systematic review and meta-analysis | Pooled analysis of RCTs                                                 | FOS increases <i>Bifidobacterium</i> abundance and improves stool frequency without notable adverse effects.                        |
| Deng et al. (2024)        | Compare efficacy of probiotics, prebiotics, synbiotics for chronic constipation | Meta-analysis                       | Bayesian network analysis of RCTs                                       | Synbiotics showed highest efficacy, followed by probiotics; prebiotics had moderate benefits.                                       |
| Wongkrasant et al. (2020) | Investigate FOS effects on tight junction assembly                              | In vitro experimental study         | Caco-2 monolayer analyses, AMPK assays                                  | FOS enhanced tight junction protein levels through AMPK activation, improving epithelial barrier function.                          |
| Liang et al. (2022)       | Evaluate anti-allergic potential of infant-derived probiotics                   | Experimental / in vivo              | Mouse models and immunological profiling                                | Two <i>Lactobacillus</i> strains reduced IgE, mast-cell activation, and airway allergic responses.                                  |
| Carlini et al. (2023)     | Review IL-10 biology and relevance in disease                                   | Review                              | Immunological pathway analysis                                          | IL-10 regulates immune homeostasis; dysregulation contributes to cancer, COVID-19, and post-COVID syndromes.                        |

| Authors (Year)             | Objectives                                                                         | Study Design                      | Methods                                                             | Key Results                                                                                                                                              |
|----------------------------|------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mann et al. (2024)         | Examine SCFAs linking diet, microbiome, immunity                                   | Comprehensive review              | Mechanistic and clinical data synthesis                             | SCFAs are key mediators of diet–immune interaction, influencing inflammation, tolerance, and systemic immunity.                                          |
| Ma et al. (2021)           | Assess probiotic effects on colitis and cognition                                  | Animal study                      | DSS-induced colitis mice, cytokine profiling                        | <i>L. rhamnosus</i> and <i>B. longum</i> improved colitis and cognitive impairment by shifting IFN- $\gamma$ /IL-10 and TNF- $\alpha$ /IL-10 ratios.     |
| Mei et al. (2022)          | Study effects of <i>L. fermentum</i> on IgA secretion                              | Experimental study                | Measurement of mucosal IgA in response to strain exposure           | IgA stimulation varied across individuals; probiotic effects dependent on host background.                                                               |
| Ramos et al. (2022)        | Review IgA role in helminthiasis                                                   | Systematic review                 | Evidence evaluation from human and animal studies                   | IgA contributes to parasite expulsion and immune modulation, but effects vary by helminth species.                                                       |
| Takeuchi & Ohno (2022)     | Evaluate IgA as regulator of commensal microbiota                                  | Review                            | Host–microbiota immunological analysis                              | IgA shapes microbial composition and supports mucosal homeostasis; deficiencies lead to dysbiosis.                                                       |
| Lisicka et al. (2024)      | Investigate IgA in enteric virus colonization                                      | Experimental immunology           | Viral colonization assays in murine models                          | IgA restricts viral colonization and preserves mucosal immune equilibrium.                                                                               |
| Zheng et al. (2022)        | Assess <i>L. rhamnosus</i> CY12 effects on barrier function                        | In vitro                          | LPS-induced Caco-2 injury, TJ protein assays                        | CY12 increased tight junction proteins, reduced oxidative stress, and lowered inflammation markers.                                                      |
| López-Almada et al. (2024) | Analyze probiotic/postbiotic effects of <i>L. rhamnosus</i> in obesity             | Review                            | Metabolic and immunological data review                             | <i>L. rhamnosus</i> reduces inflammation, modulates adipokines, and improves metabolic parameters in obesity.                                            |
| Matar et al. (2024)        | Update on intestinal barrier repair mechanisms                                     | Review                            | Multi-factorial barrier integrity synthesis                         | Highlighted roles of diet, biotics, and signaling pathways in restoring barrier function.                                                                |
| Li et al. (2025)           | Study miRNA-mediated immune modulation by probiotics                               | Review                            | Evidence on host miRNA-probiotic interactions                       | Probiotics regulate host miRNAs that influence immune signaling, inflammation, and epithelial function.                                                  |
| Virk et al. (2024)         | Examine anti-inflammatory and systemic benefits of probiotics                      | Review                            | Synthesis literature of organ-specific probiotic effects            | Probiotics showed multi-organ anti-inflammatory, metabolic, and barrier-protective effects across systems.                                               |
| Huang et al. (2021)        | Evaluate efficacy of probiotics for acute diarrhea in children                     | Systematic review & meta-analysis | Comprehensive review of clinical trials assessing probiotic therapy | Probiotics significantly reduced duration and frequency of diarrhea and improved clinical recovery.                                                      |
| Zhao et al. (2022)         | Assess probiotics for preventing acute URTI                                        | Cochrane systematic review        | Comprehensive analysis of RCTs                                      | Probiotics lowered incidence, duration, and antibiotic use for URTIs compared to placebo.                                                                |
| Voigt & Lele (2022)        | Determine whether <i>L. rhamnosus</i> prevents atopic dermatitis                   | Systematic review & meta-analysis | Pooled RCT data                                                     | Prenatal–postnatal <i>L. rhamnosus</i> significantly reduced risk of atopic dermatitis in infants.                                                       |
| Pirker & Vogl (2024)       | Review early-life immune development related to microbiota and allergy onset       | Narrative review                  | Synthesis of developmental immunology & microbiome literature       | Early gut dysbiosis disrupts immune tolerance, increasing allergy risk; balanced microbiota essential for mucosal immunity maturation.                   |
| Peng et al. (2023)         | Review clinical efficacy of <i>L. reuteri</i> in digestive diseases                | Review                            | Comprehensive summarization of clinical trials                      | <i>L. reuteri</i> effective in infant colic, diarrhea, <i>H. pylori</i> management, constipation, with anti-inflammatory and barrier-protective actions. |
| Dargenio et al. (2024)     | Assess benefits of <i>B. longum</i> subsp. <i>infantis</i> on pediatric gut health | Narrative review                  | Evaluation of clinical & mechanistic evidence                       | Strain improves gut maturation, immune modulation, reduces enteric inflammation, and enhances nutrient utilization.                                      |

| Authors (Year)                     | Objectives                                                            | Study Design                      | Methods                                                         | Key Results                                                                                                                            |
|------------------------------------|-----------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Liu et al. (2024)                  | Summarize benefits of <i>L. reuteri</i> on oral and systemic health   | Review                            | Analysis of experimental & clinical findings                    | Provides anti-inflammatory, antimicrobial, and immunomodulatory effects in oral, gastrointestinal, metabolic, and systemic conditions. |
| Yadav et al. (2022)                | Review role of pro-, pre-, synbiotics in next-gen therapeutics        | Review                            | Broad literature synthesis                                      | Demonstrated safety and therapeutic potential in immunity, metabolism, and anti-inflammatory pathways.                                 |
| Phavichitr et al. (2021)           | Assess synbiotics' effect on early-life microbiota                    | Randomized, double-blind trial    | Infant synbiotic supplementation                                | Synbiotics increased Bifidobacteria abundance and improved gut microbiota composition and stool biomarkers.                            |
| You et al. (2022)                  | Explain how prebiotics promote probiotic growth                       | Review                            | Mechanistic synthesis                                           | Prebiotics enhance probiotic colonization via selective fermentation, SCFA production, and modulation of bacterial signaling pathways. |
| Markowiak-Kopeć & Śliżewska (2020) | Evaluate probiotic effects on SCFA production                         | Review                            | Summary of microbiome-SCFA interactions                         | Probiotics increase acetate, propionate, and butyrate production, supporting gut integrity and immune modulation.                      |
| Portincasa et al. (2022)           | Examine SCFA roles in glucose homeostasis                             | Review                            | Literature synthesis of metabolic & microbiome data             | SCFAs enhance insulin sensitivity, modulate GLP-1, and regulate hepatic glucose output.                                                |
| Liu et al. (2023)                  | Review SCFA regulation in immunity                                    | Review                            | Immunological evidence synthesis                                | SCFAs regulate Treg differentiation, reduce inflammation, and strengthen epithelial defense.                                           |
| Martinez Guevara et al. (2024)     | Determine effectiveness of pro/pre/synbiotics in PCOS                 | Systematic review of RCTs         | Meta-analysis of metabolic & hormonal outcomes                  | Supplements improved insulin resistance, decreased androgen levels, and improved inflammatory markers.                                 |
| Rozé et al. (2012)                 | Compare $\alpha$ -lactalbumin + symbiotic formula vs standard formula | Multicenter RCT                   | Infant feeding intervention                                     | Synbiotic-enriched formula improved gut microbiota composition and reduced GI symptoms.                                                |
| Kim & Mills (2024)                 | Overview of pro/pre/syn/postbiotics in human health                   | Review                            | Microbiome-focused synthesis                                    | Highlights roles in metabolic, immune, GI, and neuro-behavioral health, emphasizing personalized nutrition.                            |
| Hojsak & Kolaček (2024)            | Review role of probiotics in pediatric GI conditions                  | Review                            | Literature synthesis of clinical evidence                       | Strong evidence for acute diarrhea reduction; benefits also for constipation, colic, and antibiotic-associated diarrhea.               |
| Schnadower et al. (2020)           | Assess dose, age, weight effects on probiotic response in AGE         | Secondary analysis of RCT data    | Effects of pediatric AGE probiotic treatment                    | Younger age and adequate dosing correlated with better symptom improvement; dose-response relationship observed.                       |
| García-Santos et al. (2023)        | Summary of probiotics for pediatric GI disease prevention/treatment   | Review                            | Literature synthesis of clinical trial compilation              | Probiotics reduced diarrhea incidence, improved gut barrier markers, and supported immune maturation.                                  |
| Paiandeh et al. (2024)             | Evaluate pro/pre/synbiotics in malnourished children                  | Systematic review & meta-analysis | Comprehensive analysis of anthropometric and infection outcomes | Supplements improved weight gain, height, and reduced respiratory infection episodes.                                                  |
| Guamán et al. (2024)               | Review bioactive molecules from probiotics affecting child health     | Review                            | Literature synthesis of clinical evidence                       | Postbiotics and metabolites show anti-inflammatory, antimicrobial, immunomodulatory actions beneficial for pediatric health.           |
| Abeltino et al. (2024)             | Explore gut microbiota role in precision nutrition                    | Review                            | Multi-omics synthesis                                           | Personalized dietary modulation using microbiome profiles enhances metabolic and immune outcomes.                                      |

| Authors (Year)       | Objectives                                          | Study Design | Methods                                               | Key Results                                                                                               |
|----------------------|-----------------------------------------------------|--------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Saeed et al. (2022)  | Summarize microbiota changes in childhood disorders | Review       | Literature synthesis of pediatric microbiome evidence | Dysbiosis linked to allergies, obesity, GI disorders; microbiota-targeted therapies may improve outcomes. |
| Pieren et al. (2022) | Review adaptive immune development in early life    | Review       | Analysis of immunological maturation                  | Gut microbial exposures drive balanced Th1/Th2 development and immunological tolerance.                   |

## CONCLUSIONS

Overall, prebiotics and probiotics play an essential role in supporting children's immune health, with positive impacts seen in reduced infections, improved gastrointestinal health, strengthened immune responses, and promoting well-being in children. The combination of the two, known as synbiotics, shows even greater potential in improving gut microbiota balance and boosting immunity. While the results of current studies are promising, more research is needed to understand the in-depth mechanisms, optimal dosage and long-term benefits of using prebiotics, probiotics and synbiotics. A personalized approach based on a paediatric patient's specific condition could potentially establish the foundation for more efficacious interventions supporting immune health across the lifespan.

## ACKNOWLEDGEMENT

The authors would like to express their sincere gratitude to all contributors and institutions involved in the completion of this manuscript.

## CONFLICT OF INTEREST AND FUNDING DISCLOSURE

All authors declared no conflict of interest. The authors received no external funding for this work.

## AUTHOR CONTRIBUTIONS

LBS: conceptualization, investigation, methodology, supervision, writing review & editing; CD: methodology, writing original draft, writing review & editing; DP: methodology, writing original draft, writing review & editing; IRL: writing original draft, writing review & editing. All authors have read and approved the submitted version of the manuscript.

## REFERENCES

1. Fragkou, P. C., Karaviti, D., Zemlin, M. & Skevaki, C. Impact of Early Life Nutrition on Children's Immune System and Noncommunicable Diseases Through Its Effects on the Bacterial Microbiome, Virome and Mycobiome. *Frontiers in Immunol* **12**, 644269 (2021). <https://doi.org/10.3389/fimmu.2021.644269>
2. Buonocore, G. Microbiota and gut immunity in infants and young children. *Global Pediatrics* **9**, 100202 (2024). <https://doi.org/10.1016/j.gpeds.2024.100202>
3. Xenopoulou, E., Kontele, I., Sergeantanis, T. N., Grammatikopoulou, M. G., Tzoutzou, M., Kotrokois, K., Tsitsika, A. & Vassilakou, T. Biotics and Children's and Adolescents' Health: A Narrative Review. *Children* **11**, 329 (2024). <https://doi.org/10.3390/children11030329>
4. Ignatova, I., Arsov, A., Petrova, P. & Petrov, K. Prebiotic Effects of  $\alpha$ - and  $\beta$ -Galactooligosaccharides: The Structure-Function Relation. *Molecules* 2025, Vol. 30, Page 803 **30**, 803 (2025). <https://doi.org/10.3390/molecules30040803>
5. Mazziotta, C., Tognon, M., Martini, F., Torreggiani, E. & Rotondo, J. C. Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health. *Cells* **12**, 184 (2023). <https://doi.org/10.3390/cells12010184>
6. Darma, A., Dewi, D. K., Chandra, D. N., Basrowi, R. W., Khoe, L. C., Pratiwi, D. & Sundjaya, T. The Role of Prebiotic, Probiotic, and Synbiotic in Gut Microbiota and Gut Permeability in Children Affected by Air Pollution. *Current Nutrition & Food Science* **20**, 1272–1281 (2024). <https://doi.org/10.2174/0115734013284557240108081832>
7. Li, X., Hu, S., Yin, J., Peng, X., King, L., Li, L., Xu, Z., Zhou, L., Peng, Z., Ze, X., Zhang, X., Hou, Q., Shan, Z. & Liu, L. Effect of synbiotic supplementation on immune parameters and gut microbiota in healthy adults: a double-blind randomized controlled trial. *Gut Microbes* **15**, 2247025 (2023). <https://doi.org/10.1080/19490976.2023.2247025>
8. Okolie, M. C., Edo, G. I., Ainyanbhor, I. E., Jikah, A. N., Akpogheli, P. O., Yousif, E., Zainulabdeen, K., Isoje, E. F., Igbuku, U. A., Orogu, J. O., Owheru, J. O., Essaghah, A. E. A. & Umar, H. Gut microbiota and immunity in health and diseases: a review. *Proceedings of the Indian National Science Academy* 2024 1–18 (2024). doi:10.1007/S43538-024-00355-1
9. Mpakosi, A., Sokou, R., Theodoraki, M., Iacovidou, N., Cholevas, V., Tsantes, A. G., Liakou, A. I., Drogari-Apiranthitou, M. & Kaliouli-Antonopoulou, C. The Role of Infant and Early Childhood Gut Virome in Immunity and the Triggering of Autoimmunity—A Narrative Review. *Diagnostics* 2025, Vol. 15, Page 413 **15**, 413 (2025). <https://doi.org/10.3390/diagnostics15040413>
10. Duan, H., Wang, L. J., Huangfu, M. & Li, H. The impact of microbiota-derived short-chain fatty acids on macrophage activities in disease: Mechanisms and therapeutic potentials. *Biomedicine & Pharmacotherapy* **165**, 115276 (2023). <https://doi.org/10.1016/j.biopha.2023.115276>
11. Dera, N., Kosińska-Kaczyńska, K., Żeber-Lubecka, N., Brawura-Biskupski-Samaha, R., Massalska, D., Szymusik, I., Dera, K. & Ciebia, M. Impact of Early-Life Microbiota on Immune System Development and Allergic Disorders. *Biomedicine* **13**, 121 (2025). <https://doi.org/10.3390/biomedicine13010121>
12. Yuan, C., He, Y., Xie, K., Feng, L., Gao, S. & Cai, L. Review of microbiota gut brain axis and innate immunity in inflammatory and infective diseases. *Frontiers in Cellular and Infection Microbiology* **13**, 1282431 (2023). <https://doi.org/10.3389/fcimb.2023.1282431>
13. Kasarello, K., Cudnoch-Jedrzejewska, A. & Czarzasta, K. Communication of gut microbiota and brain via immune and neuroendocrine signaling. *Frontiers in Microbiology* **14**, 1118529 (2023). <https://doi.org/10.3389/fmicb.2023.1118529>

14. Pantazi, A. C., Mihai, C. M., Balasa, A. L., Chisnoiu, T., Lupu, A., Frecus, C. E., Mihai, L., Ungureanu, A., Kassim, M. A. K., Andrusca, A., Nicolae, M., Cuzic, V., Lupu, V. V. & Cambrea, S. C. Relationship between Gut Microbiota and Allergies in Children: A Literature Review. *Nutrients* **15**, 2529 (2023). <https://doi.org/10.3390/nu15112529>
15. Yao, Y., Cai, X., Ye, Y., Wang, F., Chen, F. & Zheng, C. The Role of Microbiota in Infant Health: From Early Life to Adulthood. *Frontiers in Immunology* **12**, 708472 (2021). <https://doi.org/10.3389/fimmu.2021.708472>
16. Kim, Y. T. & Mills, D. A. Exploring the gut microbiome: probiotics, prebiotics, synbiotics, and postbiotics as key players in human health and disease improvement. *Food Science and Biotechnology* **2024 33:9 33**, 2065–2080 (2024). <https://doi.org/10.1007/s10068-024-01620-1>
17. Wiertsema, S. P., van Bergenhenegouwen, J., Garssen, J. & Knippels, L. M. J. The Interplay between the Gut Microbiome and the Immune System in the Context of Infectious Diseases throughout Life and the Role of Nutrition in Optimizing Treatment Strategies. *Nutrients* **13**, 886 (2021). <https://doi.org/10.3390/nu13030886>
18. Zheng, D., Liwinski, T. & Elinav, E. Interaction between microbiota and immunity in health and disease. *Cell Research* **2020 30:6 30**, 492–506 (2020). <https://doi.org/10.1038/s41422-020-0332-7>
19. Sadeghpour Heravi, F. Gut Microbiota and Autoimmune Diseases: Mechanisms, Treatment, Challenges, and Future Recommendations. *Current Clinical Microbiology Report* **11**, 18–33 (2024). <https://doi.org/10.1007/s40588-023-00213-6>
20. Zhang, R., Ding, N., Feng, X. & Liao, W. The gut microbiome, immune modulation, and cognitive decline: insights on the gut-brain axis. *Frontiers in Immunology* **16**, 1529958 (2025). <https://doi.org/10.3389/fimmu.2025.1529958>
21. Al Nabhani, Z. & Eberl, G. Imprinting of the immune system by the microbiota early in life. *Mucosal Immunology* **13**, 183–189 (2020). <https://doi.org/10.1038/s41385-020-0257-y>
22. Fadlyana, E., Soemarko, D. S., Endaryanto, A., Haryanto, B., Darma, A., Dewi, D. K., Chandra, D. N., Hartono, B., Buftheim, S., Wasito, E., Sundjaya, T. & Basrowi, R. W. The Impact of Air Pollution on Gut Microbiota and Children's Health: An Expert Consensus. *Children* **9**, 765 (2022). <https://doi.org/10.3390/children9060765>
23. Endaryanto, A., Darma, A., Sundjaya, T., Masita, B. M. & Basrowi, R. W. The Notorious Triumvirate in Pediatric Health: Air Pollution, Respiratory Allergy, and Infection. *Children* **10**, 1067 (2023). <https://doi.org/10.3390/children10061067>
24. Bugya, Z., Prechl, J., Szénási, T., Nemes, É., Bácsi, A. & Koncz, G. Multiple Levels of Immunological Memory and Their Association with Vaccination. *Vaccines* **9**, 174 (2021). <https://doi.org/10.3390/vaccines9020174>
25. Ney, L. M., Wipplinger, M., Grossmann, M., Engert, N., Wegner, V. D. & Mosig, A. S. Short chain fatty acids: key regulators of the local and systemic immune response in inflammatory diseases and infections. *Open Biology* **13**, 230014 (2023). <https://doi.org/10.1098/rsob.230014>
26. McBride, D. A., Dorn, N. C., Yao, M., Johnson, W. T., Wang, W., Bottini, N. & Shah, N. J. Short-chain fatty acid-mediated epigenetic modulation of inflammatory T cells in vitro. *Drug Delivery and Translational Research* **13**, 1912–1924 (2023). <https://doi.org/10.1007/s13346-022-01284-6>
27. Liu, X. F., Shao, J. H., Liao, Y. T., Wang, L. N., Jia, Y., Dong, P. J., Liu, Z. Z., He, D. D., Li, C. & Zhang, X. Regulation of short-chain fatty acids in the immune system. *Frontiers in Immunology* **14**, 1186892 (2023). <https://doi.org/10.3389/fimmu.2023.1186892>
28. Liu, H., Lu, H., Wang, Y., Yu, C., He, Z. & Dong, H. Unlocking the power of short-chain fatty acids in ameliorating intestinal mucosal immunity: a new porcine nutritional approach. *Frontiers in Cellular and Infection Microbiology* **14**, 1449030 (2024). <https://doi.org/10.3389/fcimb.2024.1449030>
29. Hsu, C. Y., Khachatryan, L. G., Younis, N. K., Mustafa, M. A., Ahmad, N., Athab, Z. H., Polyanskaya, A. V., Kasanave, E. V., Mirzaei, R. & Karampoor, S. Microbiota-derived short chain fatty acids in pediatric health and diseases: from gut development to neuroprotection. *Frontiers in Microbiology* **15**, 1456793 (2024). <https://doi.org/10.3389/fmicb.2024.1456793>
30. Ji, J., Jin, W., Liu, S. J., Jiao, Z. & Li, X. Probiotics, prebiotics, and postbiotics in health and disease. *MedComm (Beijing)* **4**, e420 (2023). <https://doi.org/10.1002/mco2.420>
31. Holmes, Z. C., Villa, M. M., Durand, H. K., Jiang, S., Dallow, E. P., Petrone, B. L., Silverman, J. D., Lin, P. H. & David, L. A. Microbiota responses to different prebiotics are conserved within individuals and associated with habitual fiber intake. *Microbiome* **10**, (2022). <https://doi.org/10.1186/s40168-022-01307-x>
32. Bevilacqua, A., Campaniello, D., Speranza, B., Racioppo, A., Sinigaglia, M. & Corbo, M. R. An Update on Prebiotics and on Their Health Effects. *Foods* **13**, 446 (2024). <https://doi.org/10.3390/foods13030446>
33. Kaewarsar, E., Chaayasut, C., Lailerd, N., Makhmrueng, N., Peerajan, S. & Sirilun, S. Optimization of Mixed Inulin, Fructooligosaccharides, and Galactooligosaccharides as Prebiotics for Stimulation of Probiotics Growth and Function. *Foods* **2023, Vol. 12, Page 1591 12**, 1591 (2023). <https://doi.org/10.3390/foods12081591>
34. Yoo, S., Jung, S. C., Kwak, K. & Kim, J. S. The Role of Prebiotics in Modulating Gut Microbiota: Implications for Human Health. *International Journal of Molecular Sciences* **2024, Vol. 25, Page 4834 25**, 4834 (2024). <https://doi.org/10.3390/ijms25094834>

35. Pujari, R. & Banerjee, G. Impact of prebiotics on immune response: from the bench to the clinic. *Immunology and Cell Biology* **99**, 255–273 (2021). <https://doi.org/10.1111/imcb.12409>
36. Gavzy, S. J., Kensiski, A., Lee, Z. L., Mongodin, E. F., Ma, B. & Bromberg, J. S. Bifidobacterium mechanisms of immune modulation and tolerance. *Gut Microbes* **15**, 2291164 (2023). <https://doi.org/10.1080/19490976.2023.2291164>
37. Simon, E., Călinoiu, L. F., Mitrea, L. & Vodnar, D. C. Probiotics, Prebiotics, and Synbiotics: Implications and Beneficial Effects against Irritable Bowel Syndrome. *Nutrients* **13**, 2112 (2021). <https://doi.org/10.3390/nu13062112>
38. Pujari, R. & Banerjee, G. Impact of prebiotics on immune response: from the bench to the clinic. *Immunology and Cell Biology* **99**, 255–273 (2021). <https://doi.org/10.1111/imcb.12409>
39. Selvamani, S., Kapoor, N., Ajmera, A., El Enshasy, H. A., Dailin, D. J., Sukmawati, D., Abomoelak, M., Nurjayadi, M. & Abomoelak, B. Prebiotics in New-Born and Children's Health. *Microorganisms* **11**, 2453 (2023). <https://doi.org/10.3390/microorganisms11102453>
40. Mirzaei, R., Bouzari, B., Hosseini-Fard, S. R., Mazaheri, M., Ahmadyousefi, Y., Abdi, M., Jalalifar, S., Karimitabar, Z., Teimoori, A., Keyvani, H., Zamani, F., Yousefimashouf, R. & Karampoor, S. Role of microbiota-derived short-chain fatty acids in nervous system disorders. *Biomedicine & Pharmacotherapy* **139**, 111661 (2021). <https://doi.org/10.1016/j.biopha.2021.111661>
41. Ma, J., Piao, X., Mahfuz, S., Long, S. & Wang, J. The interaction among gut microbes, the intestinal barrier and short chain fatty acids. *Animal Nutrition* **9**, 159–174 (2022). <https://doi.org/10.1016/j.aninu.2022.03.003>
42. Facchin, S., Bertin, L., Bonazzi, E., Lorenzon, G., De Barba, C., Barberio, B., Zingone, F., Maniero, D., Scarpa, M., Ruffolo, C., Angriman, I. & Savarino, E. V. Short-Chain Fatty Acids and Human Health: From Metabolic Pathways to Current Therapeutic Implications. *Life* **14**, 559 (2024). <https://doi.org/10.3390/life14050559>
43. Fusco, W., Lorenzo, M. B., Cintoni, M., Porcari, S., Rinninella, E., Kaitsas, F., Lener, E., Mele, M. C., Gasbarrini, A., Collado, M. C., Cammarota, G. & Ianiro, G. Short-Chain Fatty-Acid-Producing Bacteria: Key Components of the Human Gut Microbiota. *Nutrients* **15**, 2211 (2023). <https://doi.org/10.3390/nu15092211>
44. Du, Y., He, C., An, Y., Huang, Y., Zhang, H., Fu, W., Wang, M., Shan, Z., Xie, J., Yang, Y. & Zhao, B. The Role of Short Chain Fatty Acids in Inflammation and Body Health. *International Journal of Molecular Sciences* **2024**, Vol. 25, Page 7379 **25**, 7379 (2024). <https://doi.org/10.3390/ijms25137379>
45. Zhou, P., Chen, C., Patil, S. & Dong, S. Unveiling the therapeutic symphony of probiotics, prebiotics, and postbiotics in gut-immune harmony. *Frontiers in Nutrition* **11**, (2024). <https://doi.org/10.3389/fnut.2024.1355542>
46. Liu, Y., Wang, J. & Wu, C. Modulation of Gut Microbiota and Immune System by Probiotics, Pre-biotics, and Post-biotics. *Frontiers in Nutrition* **8**, 634897 (2022). <https://doi.org/10.3389/fnut.2021.634897>
47. Goswami, T. K., Singh, M., Dhawan, M., Mitra, S., Emran, T. Bin, Rabaan, A. A., Mutair, A. Al, Alawi, Z. Al, Alhumaid, S. & Dhama, K. Regulatory T cells (Tregs) and their therapeutic potential against autoimmune disorders – Advances and challenges. *Human Vaccines and Immunotherapeutics* **18**, 2035117 (2022). <https://doi.org/10.1080/21645515.2022.2035117>
48. Pedrosa, L. de F., de Vos, P. & Fabi, J. P. From Structure to Function: How Prebiotic Diversity Shapes Gut Integrity and Immune Balance. *Nutrients* **2024**, Vol. 16, Page 4286 **16**, 4286 (2024). <https://doi.org/10.3390/nu16244286>
49. Gulliver, E. L., Young, R. B., Chonwerawong, M., D'Adamo, G. L., Thomason, T., Widdop, J. T., Rutten, E. L., Rossetto Marcelino, V., Bryant, R. V., Costello, S. P., O'Brien, C. L., Hold, G. L., Giles, E. M. & Forster, S. C. Review article: the future of microbiome-based therapeutics. *Alimentary Pharmacology & Therapeutics* **56**, 192–208 (2022). <https://doi.org/10.1111/apt.17049>
50. Dewi, D. K., Adi, N. P., Prayogo, A., Sundjaya, T., Wasito, E., Kekalih, A., Basrowi, R. W. & Jo, J. Regular Consumption of Fortified Growing-up Milk Attenuates Upper Respiratory Tract Infection among Young Children in Indonesia: A Retrospective Cohort Study. *Open Public Health Journal* **17**, (2024). <https://doi.org/10.2174/0118749445290351240520104252>
51. Dou, Y., Yu, X., Luo, Y., Chen, B., Ma, D. & Zhu, J. Effect of Fructooligosaccharides Supplementation on the Gut Microbiota in Human: A Systematic Review and Meta-Analysis. *Nutrients* **14**, 3298 (2022). <https://doi.org/10.3390/nu14163298>
52. Deng, X., Liang, C., Zhou, L., Shang, X., Hui, X., Hou, L., Wang, Y., Liu, W., Liang, S., Yao, L., Yang, K. & Li, X. Network meta-analysis of probiotics, prebiotics, and synbiotics for the treatment of chronic constipation in adults. *European Journal of Nutrition* **63**, 1999–2010 (2024). <https://doi.org/10.1007/s00394-023-03241-7>
53. Wongkrasant, P., Pongkorpsakol, P., Ariyadamrongkwan, J., Meesomboon, R., Satitsri, S., Pichyangkura, R., Barrett, K. E. & Muanprasat, C. A prebiotic fructo-oligosaccharide promotes tight junction assembly in intestinal epithelial cells via an AMPK-dependent pathway. *Biomedicine & Pharmacotherapy* **129**, 110415 (2020). <https://doi.org/10.1016/j.biopha.2020.110415>
54. Liang, H., Zhang, Y., Miao, Z., Cheng, R., Jiang, F., Ze, X., Shen, X. & He, F. Anti-allergic effects of two potential probiotic strains isolated from infant

- feces in China. *Journal of Functional Foods* **92**, 105070 (2022).  
<https://doi.org/10.1016/j.jff.2022.105070>
55. Carlini, V., Noonan, D. M., Abdalalem, E., Goletti, D., Sansone, C., Calabrone, L. & Albini, A. The multifaceted nature of IL-10: regulation, role in immunological homeostasis and its relevance to cancer, COVID-19 and post-COVID conditions. *Frontiers in Immunology* **14**, (2023).  
<https://doi.org/10.3389/fimmu.2023.1223456>
56. Mann, E. R., Lam, Y. K. & Uhlig, H. H. Short-chain fatty acids: linking diet, the microbiome and immunity. *Nature Reviews Immunology* **24**, 577–595 (2024). <https://doi.org/10.1038/s41577-024-01014-8>
57. Ma, X., Shin, Y. J., Jang, H. M., Joo, M. K., Yoo, J. W. & Kim, D. H. Lactobacillus rhamnosus and Bifidobacterium longum alleviate colitis and cognitive impairment in mice by regulating IFN- $\gamma$  to IL-10 and TNF- $\alpha$  to IL-10 expression ratios. *Scientific Reports* **11**, 20659 (2021).  
<https://doi.org/10.1038/s41598-021-00244-2>
58. Mei, L., Chen, Y., Wang, J., Lu, J., Zhao, J., Zhang, H., Wang, G. & Chen, W. Lactobacillus fermentum Stimulates Intestinal Secretion of Immunoglobulin A in an Individual-Specific Manner. *Foods* **11**, 1229 (2022).  
<https://doi.org/10.3390/foods11091229>
59. Ramos, A. C. S., Oliveira, L. M., Santos, Y. L. D. C. O., Dantas, M. C. S., Walker, C. I. B., Faria, A. M. C., Bueno, L. L., Dolabella, S. S. & Fujiwara, R. T. The role of IgA in gastrointestinal helminthiasis: A systematic review. *Immunology Letter* **249**, 12–22 (2022).  
<https://doi.org/10.1016/j.imlet.2022.03.003>
60. Takeuchi, T. & Ohno, H. IgA in human health and diseases: Potential regulator of commensal microbiota. *Frontiers in Immunology* **13**, (2022).  
<https://doi.org/10.3389/fimmu.2022.1001234>
61. Lisicka, W., Earley, Z., Sifakis, J., Mattingly, J., Erickson, S., Riesenfeld, S., Cyster, J., Jabri, B. & Bendelac, A. IgA controls enteric virus colonization to preserve intestinal immune homeostasis. *The Journal of Immunology* **212**, 0392\_5110-0392\_5110 (2024).  
<https://doi.org/10.4049/jimmunol.212.suppl.0392.5110>
62. Zheng, J., Ahmad, A. A., Yang, Y., Liang, Z., Shen, W., Feng, M., Shen, J., Lan, X. & Ding, X. Lactobacillus rhamnosus CY12 Enhances Intestinal Barrier Function by Regulating Tight Junction Protein Expression, Oxidative Stress, and Inflammation Response in Lipopolysaccharide-Induced Caco-2 Cells. *International Journal of Molecular Science* **23**, 11162 (2022).  
<https://doi.org/10.3390/ijms231911162>
63. López-Almada, G., Mejía-León, M. E. & Salazar-López, N. J. Probiotic, Postbiotic, and Paraprobiotic Effects of Lactobacillus rhamnosus as a Modulator of Obesity-Associated Factors. *Foods* **2024**, Vol. 13, Page 3529 **13**, 3529 (2024).  
<https://doi.org/10.3390/foods13223529>
64. Matar, A., Damianos, J. A., Jencks, K. J. & Camilleri, M. Intestinal Barrier Impairment, Preservation, and Repair: An Update. *Nutrients* **16**, 3494 (2024).  
<https://doi.org/10.3390/nu16203494>
65. Li, W., Zeng, Y., Zhong, J., Hu, Y., Xiong, X., Zhou, Y. & Fu, L. Probiotics Exert Gut Immunomodulatory Effects by Regulating the Expression of Host miRNAs. *Probiotics and Antimicrobial Proteins* **17**, 557-568 (2025).  
Doi:10.1007/S12602-024-10443-9
66. Virk, M. S., Virk, M. A., He, Y., Tufail, T., Gul, M., Qayum, A., Rehman, A., Rashid, A., Ekumah, J. N., Han, X., Wang, J. & Ren, X. The Anti-Inflammatory and Curative Exponent of Probiotics: A Comprehensive and Authentic Ingredient for the Sustained Functioning of Major Human Organs. *Nutrients* **16**, 546 (2024).  
<https://doi.org/10.3390/nu16040546>
67. Huang, R., Xing, H. Y., Liu, H. J., Chen, Z. F. & Tang, B. B. Efficacy of probiotics in the treatment of acute diarrhea in children: a systematic review and meta-analysis of clinical trials. *Translational Pediatric* **10**, 3248-3260 (2021).  
<https://doi.org/10.21037/tp-21-511>
68. Zhao, Y., Dong, B. R. & Hao, Q. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Systematic Reviews* **2022**, CD006895 (2022).  
<https://doi.org/10.1002/14651858.CD006895.pub4>
69. Voigt, J. & Lele, M. Lactobacillus rhamnosus Used in the Perinatal Period for the Prevention of Atopic Dermatitis in Infants: A Systematic Review and Meta-Analysis of Randomized Trials. *American Journal of Clinical Dermatology* **23**, 801-811 (2022). <https://doi.org/10.1007/s40257-022-00723-x>
70. Pirker, A. L. & Vogl, T. Development of systemic and mucosal immune responses against gut microbiota in early life and implications for the onset of allergies. *Frontiers in Allergy* **5**, 1439303 (2024).  
<https://doi.org/10.3389/falgy.2024.1439303>
71. Peng, Y., Ma, Y., Luo, Z., Jiang, Y., Xu, Z. & Yu, R. Lactobacillus reuteri in digestive system diseases: focus on clinical trials and mechanisms. *Frontiers in Cellular and Infection Microbiology* **13**, 1254198 (2023).  
<https://doi.org/10.3389/fcimb.2023.1254198>
72. Dargenio, V. N., Cristofori, F., Brindicci, V. F., Schettini, F., Dargenio, C., Castellaneta, S. P., Iannone, A. & Francavilla, R. Impact of Bifidobacterium longum Subspecies infantis on Pediatric Gut Health and Nutrition: Current Evidence and Future Directions. *Nutrients* **16**, 3510 (2024).  
<https://doi.org/10.3390/nu16203510>
73. Liu, Z., Cao, Q., Wang, W., Wang, B., Yang, Y., Xian, C. J., Li, T. & Zhai, Y. The Impact of Lactobacillus reuteri on Oral and Systemic Health: A

- Comprehensive Review of Recent Research. *Microorganisms* 2025 **13**, 45 (2024). <https://doi.org/10.3390/microorganisms13010045>
74. Dargenio, V. N., Cristofori, F., Brindicci, V. F., Schettini, F., Dargenio, C., Castellaneta, S. P., Iannone, A. & Francavilla, R. Impact of *Bifidobacterium longum* Subspecies *infantis* on Pediatric Gut Health and Nutrition: Current Evidence and Future Directions. *Nutrients* **16**, 3510 (2024). <https://doi.org/10.3390/nu16203510>
75. Jeon, H. J., Seo, S., Lee, H. S., Kim, S. H., Park, J., Kim, S. E., Jung, S. A. & Moon, C. M. DOP32 Extracellular vesicles from *Bifidobacterium longum* Subspecies *infantis* attenuate intestinal inflammation via macrophage polarization. *Journal of Crohn's and Colitis* **19**, i144–i145 (2025). <https://doi.org/10.1093/ecco-jcc/jjae190.0071>
76. Yadav, M. K., Kumari, I., Singh, B., Sharma, K. K. & Tiwari, S. K. Probiotics, prebiotics and synbiotics: Safe options for next-generation therapeutics. *Applied Microbiology and Biotechnology* **106**, 505 (2022). <https://doi.org/10.1007/s00253-021-11646-8>
77. Phavichitr, N., Wang, S., Chomto, S., Tantibhaedhyangkul, R., Kakourou, A., Intarakhao, S., Jongpiputvanich, S., Wongteerasut, A., Ben-Amor, K., Martin, R., Ting, S., Suteerajintrakool, O., Visuthranukul, C., Piriyanon, P., Roeselers, G. & Knol, J. Impact of synbiotics on gut microbiota during early life: a randomized, double-blind study. *Scientific Reports* **11**, 3534 (2021). <https://doi.org/10.1038/s41598-021-83009-2>
78. You, S., Ma, Y., Yan, B., Pei, W., Wu, Q., Ding, C. & Huang, C. The promotion mechanism of prebiotics for probiotics: A review. *Frontiers in Nutrition* **9**, 1000517 (2022). <https://doi.org/10.3389/fnut.2022.1000517>
79. Markowiak-Kopeć, P. & Śliżewska, K. The Effect of Probiotics on the Production of Short-Chain Fatty Acids by Human Intestinal Microbiome. *Nutrients* **12**, 1107 (2020). <https://doi.org/10.3390/nu12041107>
80. Portincasa, P., Bonfrate, L., Vacca, M., De Angelis, M., Farella, I., Lanza, E., Khalil, M., Wang, D. Q. H., Sperandio, M. & Di Ciaula, A. Gut Microbiota and Short Chain Fatty Acids: Implications in Glucose Homeostasis. *International Journal of Molecular Science* **23**, 1105 (2022). <https://doi.org/10.3390/ijms23031105>
81. Liu, X. F., Shao, J. H., Liao, Y. T., Wang, L. N., Jia, Y., Dong, P. J., Liu, Z. Z., He, D. D., Li, C. & Zhang, X. Regulation of short-chain fatty acids in the immune system. *Frontiers in Immunology* **14**, 1186892 (2023). <https://doi.org/10.3389/fimmu.2023.1186892>
82. Verma, B., Ashique, S., Mishra, N., Kumar, N., Tyagi, N., Kumar, S., Ingawale, D., Mulgund, S. & Namdeo, A. G. Role of Synbiotics on Modulation of Inflammation. *Synbiotics in Human Health: Biology to Drug Delivery* 25–54 (2024). doi:10.1007/978-981-99-5575-6\_2
83. Martinez Guevara, D., Vidal Cañas, S., Palacios, I., Gómez, A., Estrada, M., Gallego, J. & Liscano, Y. Effectiveness of Probiotics, Prebiotics, and Synbiotics in Managing Insulin Resistance and Hormonal Imbalance in Women with Polycystic Ovary Syndrome (PCOS): A Systematic Review of Randomized Clinical Trials. *Nutrients* **16**, 3916 (2024). <https://doi.org/10.3390/nu16173916>
84. Singha, B., Singh, V. & Soni, V. Alternative therapeutics to control antimicrobial resistance: a general perspective. *Frontiers in Drug Discovery* **4**, 1385460 (2024). <https://doi.org/10.3389/fdd.2024.1385460>
85. Rozé, J. C., Barbarot, S., Butel, M. J., Kapel, N., Waligora-Dupriet, A. J., De Montgolfier, I., Leblanc, M., Godon, N., Soulaïnes, P., Darmaun, D., Rivero, M. & Dupont, C. An  $\alpha$ -lactalbumin-enriched and symbiotic-supplemented v. a standard infant formula: a multicentre, double-blind, randomised trial. *British Journal of Nutrition* **107**, 1616–1622 (2012). <https://doi.org/10.1017/S0007114512000184>
86. Chanda, S., Bonde, G. V., Tiwari, R. K. & Bishnoi, A. Synergistic Welfare of Synbiotic Nutraceuticals on Chronic Respiratory Diseases. *Synbiotics in Human Health: Biology to Drug Delivery* 535–549 (2024). [https://doi.org/10.1007/978-981-99-5575-6\\_27](https://doi.org/10.1007/978-981-99-5575-6_27)
87. Kim, Y. T. & Mills, D. A. Exploring the gut microbiome: probiotics, prebiotics, synbiotics, and postbiotics as key players in human health and disease improvement. *Food Science and Biotechnology* **33**, 2065–2080 (2024). <https://doi.org/10.1007/s10068-024-01620-1>
88. Hojsak, I. & Kolaček, S. Role of Probiotics in the Treatment and Prevention of Common Gastrointestinal Conditions in Children. *Pediatric Gastroenterology and Hepatology Nutr* **27**, 1–14 (2024). <https://doi.org/10.5223/pghn.2024.27.1.1>
89. Schnadower, D., Sapien, R. E., Casper, T. C., Vance, C., Tarr, P. I., O'Connell, K. J., Levine, A. C., Roskind, C. G., Rogers, A. J., Bhatt, S. R., Mahajan, P., Powell, E. C., Olsen, C. S., Gorelick, M. H., Dean, J. M. & Freedman, S. B. Association between Age, Weight, and Dose and Clinical Response to Probiotics in Children with Acute Gastroenteritis. *Journal of Nutrition* **151**, 65 (2020). <https://doi.org/10.1093/jn/nxz252>
90. García-Santos, J. A., Nieto-Ruiz, A., García-Ricobaraza, M., Cerdó, T. & Campoy, C. Impact of Probiotics on the Prevention and Treatment of Gastrointestinal Diseases in the Pediatric Population. *International Journal of Molecular Science* **24**, 9427 (2023). <https://doi.org/10.3390/ijms24119427>
91. Paiandeh, M., Maghalian, M., Mohammad-Alizadeh-Charandabi, S. & Mirghafourvand, M. The effect of probiotic, prebiotic, and synbiotic supplements on anthropometric measures and respiratory infections in malnourished children: a

- systematic review and meta-analysis of randomized controlled trials. *BMC Pediatrics* **24**, 702 (2024). <https://doi.org/10.1186/s12887-024-05179-y>
92. Guamán, L. P., Carrera-Pacheco, S. E., Zúñiga-Miranda, J., Teran, E., Erazo, C. & Barba-Ostria, C. The Impact of Bioactive Molecules from Probiotics on Child Health: A Comprehensive Review. *Nutrients* **16**, 3706 (2024). <https://doi.org/10.3390/nu16213706>
  93. Abeltino, A., Hatem, D., Serantoni, C., Riente, A., De Giulio, M. M., De Spirito, M., De Maio, F. & Maulucci, G. Unraveling the Gut Microbiota: Implications for Precision Nutrition and Personalized Medicine. *Nutrients* **16**, 3806 (2024). <https://doi.org/10.3390/nu16223806>
  94. Saeed, N. K., Al-Beltagi, M., Bediwy, A. S., El-Sawaf, Y. & Toema, O. Gut microbiota in various childhood disorders: Implication and indications. *World Journal of Gastroenterology* **28**, 1875 (2022). <https://doi.org/10.3748/wjg.v28.i18.1875>
  95. Pieren, D. K. J., Boer, M. C. & Wit, J. de. The adaptive immune system in early life: The shift makes it count. *Front Immunol* **13**, 1031924 (2022). <https://doi.org/10.3389/fimmu.2022.1031924>
  96. Maftei, N. M., Raileanu, C. R., Balta, A. A., Ambrose, L., Boev, M., Marin, D. B. & Lisa, E. L. The Potential Impact of Probiotics on Human Health: An Update on Their Health-Promoting Properties. *Microorganisms* **12**, 234 (2024). <https://doi.org/10.3390/microorganisms12020234>