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Review

Impact of Gut Microbiota on Immune System Regulation: A Narrative Review

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Abstract: The microbiota plays an essential role in the regulation of the natural immune system, influencing both innate and adaptive immunological responses. This review extracted information from available observational studies that explore the intricate cooperation between gut microbiota and immune system regulation across various health conditions, including Crohn's disease, respiratory infections, autoimmune diseases, cancer, metabolic disorders, and infectious diseases. Key findings highlight how dysbiosis, a rotation in the microbiome composition or microbial imbalance, contributes to disease pathogenesis and immune dysregulation, while specific microbial taxa and their metabolites can serve as potential biomarkers and therapeutic targets. By analyzing these studies, the paper aims to provide a comprehensive understanding of the gut microbiota's impact on immune function and its potential implications for disease prevention and management. In conclusion, this review comprehensively elucidates the complex relationship between gut flora and immune system regulation across various health conditions. The synthesized findings underscore the profound impact of microbiota composition on immune responses, from influencing disease susceptibility and severity to potential therapeutic interventions. Key insights include the identification of microbiota-based biomarkers for predicting treatment outcomes and disease risks, highlighting the potential for personalized medicine approaches. However, the few available observational studies, such as study design variability and the complex nature of microbiota dynamics, necessitate further mechanistic research to validate causal relationships and optimize clinical applications. Moving forward, integrating microbiota-targeted therapies and dietary interventions tailored to individual microbial profiles holds promise for mitigating immune dysregulation and improving overall health outcomes.

Keywords: Autoimmune; Cytokine; Microbiota; Mucosal immunity

1. Introduction

The human gut microbiota, a complex of various trillions of microorganisms and over 35,000 bacterial species [1], living in the digestive tract, is critical for supporting overall health. Disturbances in the composition of these species are known as dysbiosis [2]. Microbiota are engaged in various essential roles, such as digestion, nutrient ab-

sorption, and the production of vitamins and other bioactive compounds. The combined genetic material of microbiota is referred to as the microbiome [3]. Notably, the microbiota is integral to the progress and modulation of the owner's immune system [4]. The immune system, including innate and adaptive components, serves as the body's protection mechanism against pathogens [5]. Innate immunity provides the first line of defense through the release of cytokines, complement, and chemokines, as well as neutrophils and macrophages to overcome pathogenic agents [6]. Adaptive immunity, characterized by specificity and memory, involves the activation of white blood cell subtypes, such as T and B lymphocytes, that react to certain antigens [7]. The control of the immune system is a highly coordinated process involving cellular and molecular interactions to maintain immune homeostasis and prevent inappropriate inflammatory responses. Recent studies have elucidated the significant influence of gut microbiota on immune system regulation [8]. The microbiome impacts on the maturation and activities of immune cells, contributes to the development of immune regulation, and helps modulate the inflammation cascade [9]. Imbalanced gut microbiota, or the disruption of the normal gut microbiota, has been connected with various immune-mediated conditions such as inflammatory bowel disease, autoimmune disorders, and even certain cancers [10]. Investigating the bidirectional correlation between the gut microbiota and the immune system is crucial for identifying potential management strategies to enhance immune health and prevent diseases.

This review intends to offer a thorough and detailed analysis of observational studies that examine the impact of gut microbiota on immune system regulation. By analyzing findings from research on different health conditions, including Crohn's disease, respiratory infections, autoimmune diseases, and others, this paper seeks to highlight the role of certain microbial taxa and their biological compounds in immune modulation. Additionally, the review will discuss the potential of microbiota-based biomarkers and interventions in predicting and managing immune-related diseases. The ultimate goal is to enhance our understanding of gut microbiota-immune system connections and their implications for disease prevention and treatment.

2. Development and Influence of Microbiota

This section explores the critical early stages of microbiota formation and its profound influence on human health. The development of gut microbiota begins at birth and is altered by factors such as the mode of delivery, breastfeeding, diet, and environmental exposures. This initial colonization period is crucial as it establishes a balanced microbiome that supports immune system maturation, metabolism, neurodevelopment, and the stabilization of the intestinal barrier. Disruptions during this developmental phase can have long-term health consequences, increasing susceptibility to various diseases. This section highlights the importance of fostering a healthy microbiome from early life onwards, emphasizing the dynamic relationships between the gut microbiota and host biology and their implications for overall health.

2.1. Early Development of Gut Microbiota and Immune Health

The early development of gut microbiota is a pivotal process that significantly influences immune health throughout life. Francino [11] and Martin et al. [12] provide comprehensive insights into this critical period. In the first study, researchers emphasize that the initial colonization of the gut microbiota is shaped by factors such as the mode of delivery (vaginal birth versus cesarean section), breastfeeding, antibiotic exposure, and environmental factors. Jiménez et al. [13] have examined healthy neonates' meconium samples. According to inclusion criteria 21 newborns were selected and their meconium was obtained for further culturing. Overall, culturing appropriate dilutions of meconium samples resulted in bacterial proliferation. These early influences determine the diversity and stability of the microbiome, which in turn impacts the development of the immune system [11]. Martin et al. [12] further elucidate that the gut microbiota facilitates the maturation of the immune system by promoting the development of gut-associated lymphoid tissues (GALT) and the production of essential immune cells and molecules, such as regulatory T cells and immunoglobulins. The importance of early microbial exposure cannot be overstated. The initial exposure to a diverse array of microbes during infancy plays a critical role in educating the immune system to differentiate between harmless antigens and potential pathogens. This microbial exposure helps to establish immunological tolerance and prevents the development of inappropriate immune responses that can lead to allergic and autoimmune diseases. Early disturbances in the microbiota, such as those caused by cesarean delivery, lack of breastfeeding, or antibiotic use, can disrupt this crucial education process, leading to a higher risk of chronic

inflammatory conditions and metabolic diseases later in life.

To support the healthy formation and evolution of the microbiota, and ensure optimal immune system development, several strategies have been proposed. Promoting natural childbirth and breastfeeding are foundational steps that provide infants with beneficial microbial exposures. Additionally, the use of prebiotics and probiotics has been suggested to enhance microbiota diversity and function. Prebiotics, which are indigestible food elements, specifically promote the growth and activity of beneficial bacteria. Probiotics, on the other hand, are live beneficial bacteria that can be supplemented to restore and maintain a healthy microbiome. These strategies aim to establish a robust and balanced microbiota, thereby supporting the development of a resilient immune system capable of protecting against a wide range of diseases.

Figure 1 illustrates the typical composition of microbiota in healthy individuals compared to diseased states such as autoimmune diseases, cancer, and metabolic disorders, designed using five multinational data sources [14]. In healthy individuals, *Firmicutes* and *Bacteroidetes* dominate comprising approximately 40% and 30% of the microbiota, respectively, followed by *Actinobacteria*, *Proteobacteria*, and other minor taxa [15]. In contrast, in diseased states, there is a notable shift with reduced *Firmicutes* and *Bacteroidetes* percentages, potentially indicating dysbiosis [16]. This dysbiosis is characterized by increased *Proteobacteria* or other taxa, which can negatively impact immune responses. The diagram visually highlights these compositional changes, emphasizing how changes in microbiota composition are related to various health conditions, thereby underscoring the significance of maintaining microbial equilibrium. in maintaining immune homeostasis and overall health.

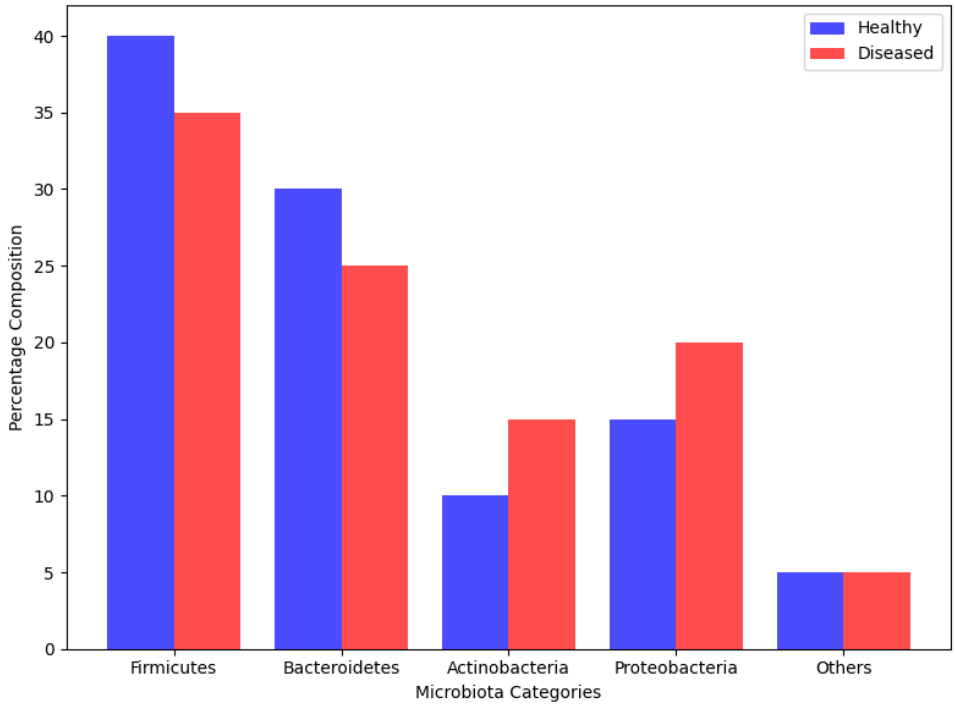

Figure 1. Diagram of microbiota composition.

2.2. Microbiota-Immune Interactions and Immune Development

Round and Mazmanian [17] and Hrncir et al. [18] provide critical insights into the complex relationships between the intestinal microbiome and the immune system, highlighting their role in immune system maturation. Round and Mazmanian [17] demonstrate that the microbiota significantly influences the development and functioning of the adaptive immune system. They reveal that the colonization of the gut by commensal bacteria after birth is essential for the maturation of immune cells, particularly regulatory T-cells, which are crucial for preserving immune balance and preventing inappropriate inflammatory responses. Hrncir et al. [18] further elucidate that the existence of microbiota, along with dietary lipopolysaccharides (LPS), promotes the proliferation of B and T cells in

key immune sites such as Peyer's patches and mesenteric lymph nodes, enhancing cytokine production and immune function. The role of microbiota in immune system maturation is profound. These microorganisms influence the immune environment by promoting the differentiation and activation of various immune cell populations. The relationships between microbial antigens and host immune cells are pivotal for the development of a balanced immune response, capable of defending against pathogens while tolerating harmless antigens. The absence or alteration of these microbial signals, as observed in germ-free or antibiotic-treated models, leads to significant deficiencies in immune cell development and function, underscoring the essential nature of microbiota in immune education and competence. Modern practices, such as cesarean sections, formula feeding, and widespread antibiotic use, have a substantial effect on the microbiota composition, with possible outcomes for immune development. These practices often result in a reduced diversity of microbiota and the loss of beneficial microbial species. The disruption of the natural microbial colonization process can cause microbial imbalance, characterized by a disruption in the microbial community that predisposes individuals to immune dysregulation and inflammatory diseases. The findings from Round and Mazmanian [17] and Hrncir et al. [18] highlight the need for strategies to preserve or restore healthy microbiota composition in the face of these modern interventions, thereby supporting optimal immune system maturation and lowering the likelihood of immune-related diseases.

Figure 2 illustrates the processes through which microbiota exert influence on immune responses. It highlights three main pathways: mucosal immunity, systemic inflammation, and adaptive immune responses. Firstly, in mucosal immunity, the diagram shows how microbiota interact with epithelial cells and mucus layers, crucial for maintaining intestinal barrier integrity. Additionally, microbiota contribute to the secretion of antimicrobial peptides and immunoglobulin A (IgA), which play pivotal roles in local defense mechanisms. Secondly, the diagram depicts systemic inflammation pathways affected by microbiota, emphasizing their role in modulating cytokine production such as TNF-α, IL-6, and IL-10, which are key mediators in inflammatory reactions. Microbiota also influence inflammatory signaling pathways like NF-κB, further impacting systemic immune responses. Lastly, the flowchart outlines adaptive immune responses influenced by microbiota, including regulation of T-cell differentiation (Th1, Th2, Tregs) and modulation of antigen presentation through major histocompatibility complex (MHC) classes I and II. These interactions are critical in shaping immune tolerance, response to pathogens, and maintenance of overall immune homeostasis. Overall, the flowchart succinctly illustrates how microbiota engage with different components of the immune system, highlighting their multifaceted role in immune regulation across mucosal, systemic, and adaptive immunity pathways.

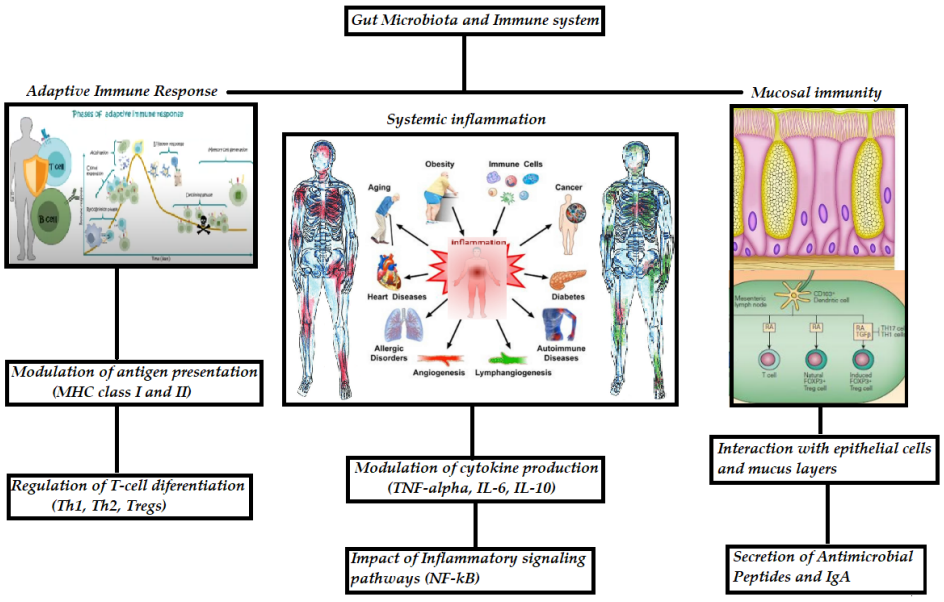

Figure 2. Flowchart of microbiota influence on immune regulation.

3. Microbiota and Specific Diseases

Microbiota's sophisticated interaction with the immune system acts as an essential role in the pathogenesis and development of several diseases. The present section explores the impact of microbiota on specific disorders, including inflammatory bowel diseases (IBD), autoimmune disorders, metabolic illnesses, respiratory infections, and cancer [19]. Through observational studies, researchers have identified significant imbalances in microbiome components and consequences associated with these conditions. Comprehending how dysbiosis contributes to disease mechanisms provides conclusions into potential diagnostic biomarkers and cure interventions that focus on the microbiota to restore health and improve clinical outcomes.

3.1. Microbiota and Crohn's Disease

This section explores in depth the intricate relationship between microbiota and Crohn's disease (CD), focusing on findings elucidated by Sanchis-Artero et al. [20]. CD, a persistent inflammatory condition impacting the digestive tract, poses substantial therapeutic challenges. The study by Sanchis-Artero et al. [20] conducted on 88 cases compromising 44 patients with CD compared to 44 healthy subjects with similar lifestyle and nutritional habits examines how anti-TNFα therapies like infliximab and adalimumab improve the composition and functional dynamics of microbiota over a rigorous six-month treatment period. Their research reveals profound alterations in microbial diversity and abundance following treatment, underscoring the microbiota's pivotal role in disease modulation. Key to their discoveries are identified biomarkers, particularly the ratios of *Faecalibacterium prausnitzii* to *Escherichia coli* and *Clostridium coccoides*, which emerge as potential markers of treatment efficacy. These biomarkers not only provide critical insights into therapeutic efficacy but also propose personalized strategies for managing CD. By comprehending how anti-TNFα therapies reshape the microbiome landscape, clinicians are empowered to tailor treatments to individual patient profiles, thereby optimizing therapeutic outcomes and potentially mitigating disease morbidity. This study highlights a paradigmatic shift in CD management, emphasizing the complex relationship between treatments and the microbiota. Beyond conventional immunological targets such as TNFα suppression, the study underscores the microbiota's nuanced influence on disease progression and treatment efficacy. Insights into microbial biomarkers lay the foundation for further research and therapeutic use, aiming to refine therapeutic strategies through personalized medicine approaches that integrate microbiota-based diagnostics and therapeutics. Zhuang et al. [21] performed a meta-analysis including 12 studies to find out the possible correlation between targeting microbiota and CD, and showed that observing microbiota could be encouraging in avoiding the post-operative recurrence of CD. They also pointed out that surgery-induced recolonization of microbiota may lead to post-surgery recurrence of the disease due to obtaining pathogenic bacteria or losing bacteria responsible for short-chain fatty acids production. Sankarasubramanian et al. [14] conducted a systematic review and meta-analysis of five multinational data sets to assess the association between microbiota and CD compared to healthy controls, and found that observing microbiota may help in understanding the etiology of CD, and introducing novel prognostic and therapeutic strategies as well. Horwat et al. [22] performed a systematic review including major indexing databases, screening 239 potential studies and finally including 9 research studies compromising a total of 118 cases, to assess the impact of exclusive enteral nutrition on microbiota in patients with CD and found that this nutritional intervention may have a beneficial influence on microbiome, but not on clinical improvement and the remission of CD.

3.2. Microbiota and Respiratory Infections in the Elderly

Fuentes et al. [23] conducted an in-depth observational study on the role of microbiota composition and susceptibility in around 25,000 older adults with influenza-like illnesses (ILI), revealing critical insights into the microbial determinants of respiratory health. Their study demonstrated that elderly individuals diagnosed with ILI exhibited significant disturbance in their microbiota compared to healthy persons. Specifically, a significant abundance of *Bacteroidetes* and *Proteobacteria*, coupled with a marked decrease in *Firmicutes* were detected. This dysbiosis was associated with heightened concentrations of pro-inflammatory agents, suggesting a widespread inflammatory condition that may increase vulnerability to respiratory infections. Among the altered bacterial taxa, *Ruminococcus torques* was particularly linked to pro-inflammatory profiles, providing crucial insights as a biomarker for inflammation and infection susceptibility. Their findings highlight the intricate interplay between microbiota and immune

function, particularly in the framework of age-related susceptibility to respiratory infections. The study also posits that the microbiota composition can significantly impact the host's immune system, consequently affecting the likelihood of developing ILI. This is of particular importance for the elderly, whose immune systems are often compromised due to aging. The research suggests that interventions focused on improving microbiota composition—such as probiotics, prebiotics, or dietary adjustments—could potentially enhance immune function and reduce the frequency of respiratory infections in the aging population. Moreover, the identification of specific microbial signatures associated with increased infection risk provides a foundation for developing microbiota-based diagnostic tools and personalized therapeutic strategies, ultimately improving respiratory health outcomes in this vulnerable population.

3.3. Microbiota and Autoimmune Diseases

Rizzetto et al. [24] conducted a comprehensive review highlighting the critical role of microbiota in the development of autoimmune diseases (AID). Their findings underscored that dysbiosis, or the imbalance in microbiota, significantly contributes to the development and progression of AID. Dysbiosis disrupts the intricate balance of the immune system, resulting in persistent systemic inflammation which is a hallmark of autoimmune conditions. The review detailed how specific microbial metabolites and their associations with the host's immune system can either exacerbate or ameliorate inflammatory responses, thereby affecting the onset and severity of autoimmune diseases. The research also pointed to the importance of targeting microbiota as a therapeutic approach for managing AID, emphasizing the need for personalized strategies based on individual microbiota profiles. Additionally, Rizzetto et al. [24] identified gender-specific differences in the interactions between the gut ecosystem and immunity, which have potential implications for the prevalence and manifestation of autoimmune diseases. They noted that hormonal differences, particularly estrogen levels, could influence microbiota composition and its subsequent impact on immune function. These gender-specific interactions might explain why certain autoimmune diseases are more prevalent in one gender compared to the other. The review suggested that understanding these differences is crucial for developing gender-specific treatments and preventive measures for autoimmune diseases. Overall, the study highlighted the complex and multifaceted interaction between microbiota, immune regulation, and autoimmune disorders, resulting in accelerated innovative microbiota-based treatment programs.

3.4. Microbiota and Cancer

Cancer is one of the leading causes of mortality in the world. As the World Health Organization (WHO) expects, by the year 2030, more than 21 million new cases of cancer and over 13 million fatalities caused by cancer will occur worldwide [25]. Disruption in microbiota in patients with colon cancer has been found in many studies. What is controversial is whether cancer is the product of a change in the microbiota or whether the progression of cancer causes changes in the natural microbiome. There is a strong argument for both theories [26]. Ge et al. [27] conducted an in-depth study examining the close cooperation between microbiota and cancer, revealing significant insights into how dysbiosis can contribute to tumorigenesis. Their research demonstrated that changes in the microbiota composition, or dysbiosis, lead to immune dysregulation and chronic inflammation, both of which are critical factors in cancer development. Specifically, dysbiosis can disrupt the normal regulatory mechanisms of the immune system, promoting a pro-inflammatory environment that fosters tumor growth and progression. The study highlighted that certain microbial metabolites produced during dysbiosis can interfere with immune checkpoints and promote an immunosuppressive tumor microenvironment, facilitating cancer cell evasion from immune surveillance. Furthermore, Ge et al. [27] discussed potential therapeutic strategies that leverage the interaction between microbiota and the immune system to combat cancer. They explored the effectiveness of probiotics, prebiotics, and dietary changes to restore a healthy microbiota balance, thereby improving immune function and reducing inflammation. Additionally, the study suggested that fecal microbiota transplantation (FMT) and microbiota-derived metabolites could be incorporated into conventional cancer treatments to improve their efficacy. By targeting the microbiota, these interventions aim to improve the immune response, reduce chronic inflammation, and inhibit tumor development. The findings underscore the importance of understanding microbiota-host interactions in cancer and promote innovative microbiome-based therapeutic strategies that could complement existing cancer treatments. Microbiota can promote cancer by various processes, including inducing a chronic inflammatory disease or immune response, altering stem cell dynamics, biosynthesis of toxic and genotoxic metabolites, and influencing host metabolism or

prevent cancer by producing its own metabolites and enzymes [28].

3.5. Gut Microbiota and Metabolic and Autoimmune Diseases

This section examines the complex relationships between microbiota and the onset of various metabolic and autoimmune disorders. The gut microbiota, comprising trillions of microorganisms, plays a critical role in sustaining metabolic homeostasis and regulating immune responses. Disruptions in the balance of these microbial communities, known as dysbiosis, have been implicated in the pathogenesis of metabolic disorders such as diabetes and obesity, as well as autoimmune diseases like rheumatoid arthritis and type 1 diabetes. This section will examine the mechanisms through which gut microbiota affects metabolic pathways and immune regulation, highlighting the potential for microbiota-targeted therapies to mitigate these diseases. Key findings from observational studies will be discussed to provide a comprehensive understanding of how gut microbiota modulates disease processes and the implications for treatment strategies. The disbalance of gut microbiome composition may initiate autoimmune diseases through the following mechanisms. Bacterial antigens may boost intestinal immune cells after encouraging a leaky gut, producing autoreactive cells, which then go systematically to the peripheral organs they are targeting and launch an assault.

3.6. Type 1 Diabetes and Microbiota

In examining the relationship between Type 1 Diabetes (T1D) and gut microbiota, De Groot et al. [29] and Liu et al. [30] provide significant insights into the alterations in microbial composition associated with the disease. De Groot et al. found that individuals with T1D exhibit a distinct gut microbiota profile compared to healthy controls, notably characterized by a reduction in butyrate-producing bacteria. This alteration is related with elevated markers of gut and systemic inflammation, indicating a potential role of gut microbiota in the pathogenesis and progression of T1D. The study highlights that butyrate, a short-chain fatty acid (SCFA), plays an essential role in regulating immune functions and maintaining intestinal barrier integrity, suggesting that the observed microbial shifts may contribute to the autoimmune processes underlying T1D. Liu et al. [30] further elaborate on these findings by identifying specific microbial taxa correlated with fasting blood glucose (FBG) levels in children with T1D. The study reports an increase in bacterial variety and significant changes in the abundance of certain taxa, such as *Bacteroides vulgatus* and *Bacteroides ovatus*, which show strong associations with FBG levels. These microbial shifts suggest potential non-invasive biomarkers for diagnosing and monitoring T1D. Moreover, the therapeutic potential of SCFA-producing bacteria is underscored by their ability to modulate immune responses and reduce inflammation. Targeting these bacteria through dietary changes, probiotics, or fecal microbiota transplantation (FMT) may provide innovative approaches for managing T1D, emphasizing the need for further research to optimize such microbiota-based therapies.

3.7. Systemic Inflammation and Autoimmunity

In the realm of systemic inflammation and autoimmune diseases, Clemente, Manasson and Scher [31] and H.J. Wu and E. Wu [8] provide a thorough understanding of the complex relationship between gut microbiota composition, immune system modulation, and disease pathogenesis. Clemente et al. [31] emphasize that dysbiosis, characterized by shifts in the gut microbial community composition and function, plays a pivotal role in triggering and perpetuating systemic inflammation. This dysregulation can disrupt intestinal barrier integrity, facilitating the translocation of microbial metabolites into systemic blood circulation. These microbial products, such as lipopolysaccharides (LPS) and peptidoglycans, activate immunocytes like macrophages and dendritic cells, leading to heightened inflammatory responses implicated in autoimmune diseases. Moreover, Clemente et al. highlight the role of metabolites produced by the microbiota, such as short-chain fatty acids (SCFAs) and bile acids, in immune regulation. SCFAs, produced by commensal bacteria through the breakdown of dietary fibers via fermentation, exert anti-inflammatory effects by encouraging the differentiation of regulatory T cells and suppressing the production of pro-inflammatory cytokines. Conversely, dysbiosis-induced reductions in SCFA-producing bacteria may compromise this regulatory mechanism, exacerbating immune dysregulation and autoimmune pathology. H.J. Wu and E. Wu [8] further underscore the influence of microbiota on immune homeostasis and autoimmune disorders through their study of both human and animal studies. They elucidate that gut microbial communities modulate host immune responses via various mechanisms, including antigen presentation, Toll-like receptor signaling, and

metabolite production. Dysbiosis can skew this delicate balance towards pro-inflammatory responses, promoting chronic inflammation and autoimmunity. The authors discuss how microbial dysbiosis in autoimmune diseases like rheumatoid arthritis and multiple sclerosis correlates with altered immune cell profiles and cytokine imbalances, perpetuating tissue damage and disease progression. Furthermore, Wu & Wu emphasize the impact of environmental factors, particularly dietary habits, on gut microbiota composition and immune function [8]. Dietary components not only serve as substrates for microbial metabolism but also directly influence host immune responses. For instance, diets rich in fiber promote the growth of beneficial bacteria that produce SCFAs, contributing to mucosal barrier integrity and immune tolerance. Conversely, diets low in fiber and high in saturated fats may foster dysbiosis and increase intestinal permeability, facilitating immune activation and systemic inflammation. Understanding these diet-microbiota-immune interactions is pivotal for developing personalized dietary interventions aimed at mitigating autoimmune disease risks and improving therapeutic outcomes.

3.8. Microbiota and Immune Function in Infectious Diseases

The passage on "Intestinal microbiota and Immune Function in Infectious Diseases" explores the nuanced interplay between gut microbiota and immune responses during infectious challenges. Commensal microorganisms contribute significantly to mucosal and systemic immune homeostasis by bolstering barrier function and fostering immune tolerance. Conversely, dysbiosis, characterized by microbial imbalance or depletion of beneficial species, can compromise immune defenses and exacerbate susceptibility to infections. Key studies underscore how specific microbial communities interact with immune cells, cytokines, and signaling pathways to modulate host responses against pathogens. Insights into products produced by microbes, such as bile acids and short-chains fatty acids, illuminate their role in regulating immune activation and inflammation during infections. By elucidating these mechanisms, the purpose of this section is to offer a thorough comprehension of how microbiota influence immune function in infectious diseases, highlighting potential avenues for microbiome-based therapeutic interventions to mitigate infection-related immune dysregulation.

3.9. COVID-19 and Microbiota

The relationship between the intestinal microbiome and COVID-19 has emerged as a significant area of research, revealing profound alterations in microbial diversity and composition among infected individuals, as elucidated by Yeoh et al. [32]. This study highlights a notable reduction in commensal bacteria, particularly those associated with butyrate and other short-chain fatty acids, which are critical for preserving the integrity of the intestinal barrier and adjusting the immune system's reaction. Concurrently, there is an increase in opportunistic pathogens, indicating a dysbiotic shift that may exacerbate systemic inflammation observed in severe COVID-19 cases. Increased concentrations of pro-inflammatory cytokines and inflammatory indicators such as C-reactive protein (CRP) further underscore the role of dysbiosis in exacerbating COVID-19 severity and complicating recovery trajectories. Furthermore, the persistence of gut microbiota dysregulation post-recovery suggests potential implications for long-term health outcomes, including the manifestation of persistent symptoms in individuals experiencing "long COVID." Yeoh et al. [32] discuss how dysbiosis may contribute to prolonged immune activation and chronic inflammation, perpetuating systemic health challenges beyond acute infection. The two-way communication between microbiota and the immune system, particularly through the gut-lung axis, underscores the microbiome's critical role in modulating respiratory mucosal immunity. This interaction influences susceptibility to severe infections of the respiratory system such as COVID-19 and highlights the effectiveness of therapy with microbiota-targeted interventions in managing disease severity and promoting immune resilience. Moreover, insights from Yeoh et al. [32] emphasize the need for individualized approaches in microbiome-based therapies to restore microbial homeostasis and mitigate COVID-19-associated complications effectively. Strategies focusing on probiotics, prebiotics, or transferring fecal microbiota from healthy donors to patients may offer approaches for modulating immune responses and enhancing mucosal defenses against viral infections. Potential avenues for further study should seek to clarify the mechanistic underpinnings of microbiota-immune interactions in COVID-19, opening the door for creative treatment approaches that leverage the potential of the gut microbiota to improve clinical outcomes and mitigate long-term sequelae.

Figure 3 illustrates the relationships observed in various studies between microbiota diversity indices (such as alpha and beta diversity) and disease severity or immune biomarkers. Each data point represents a specific

study or group within a study, showing how higher microbiota diversity tends to correlate with healthier states or lower disease severity, while lower diversity correlates with more severe disease outcomes or dysregulated immune responses. This graphical representation highlights the consistent trend across different research contexts, suggesting that microbiota composition plays an essential part in preserving immune homeostasis and influencing illness progression. Researchers can utilize such graphs to identify patterns and further investigate the mechanisms through which microbiota diversity impacts immune function and disease outcomes, thereby guiding future therapeutic interventions and microbiome-targeted treatments.

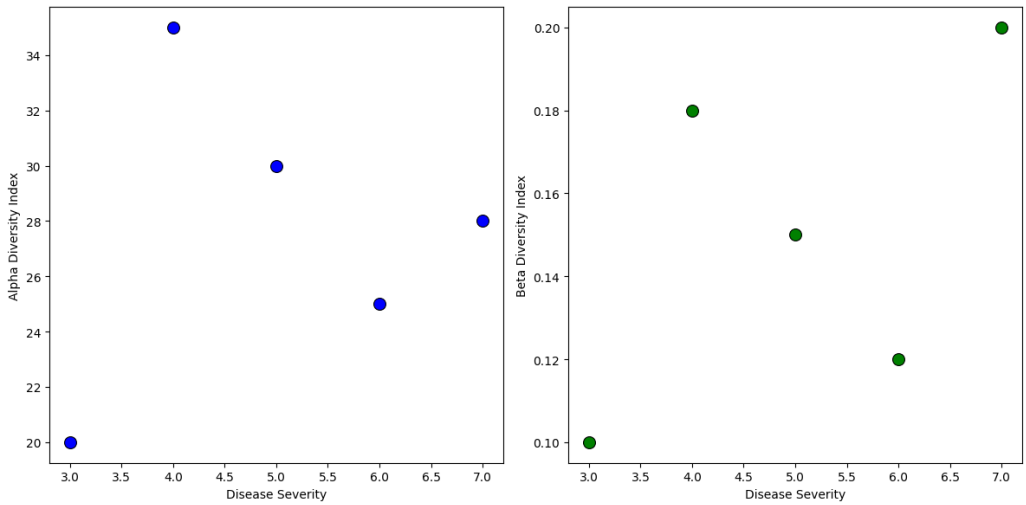

Figure 3. Correlations between microbiota diversity indices and disease severity: Visualizing relationships in gut microbiota research.

4. Immune Reconstitution in HIV/AIDS

The research by Geng et al. [33] investigates the intricate interaction between the gut microbiome and immune reconstitution in individuals infected with HIV-1. The findings underscore a profound reduction in microbial diversity as a defining feature of dysbiosis and altered composition in HIV/AIDS patients, particularly those with advanced disease stages. This dysbiosis is associated with impaired gut barrier function which results in persistent immunological activation and microbial translocation, which perpetuate systemic inflammation and immune depletion. Importantly, the reduction in the number of helpful microorganisms, such as *Lactobacillus* and *Bifidobacterium* species, correlates with poor immune recovery markers, including CD4+ T cell counts and viral load suppression during antiretroviral therapy (ART). Geng et al. [33] highlight the potential role of the intestinal microbiome in adjusting immunological responses in mucosal tissues and systemic immune reconstitution post-ART initiation. The restoration of microbial diversity and beneficial species, facilitated by interventions like probiotics, prebiotics, or FMT, emerges as a promising approach to therapy to enhance immune recovery and mitigate chronic inflammation in HIV/AIDS patients [34]. It would be worthwhile to highlight which would be the safest techniques for recomposing the microbiota in HIV patients, given the risk of excessive consumption of probiotics by this population. Serrano-Villar et al. [34] estimated that one of the safe and effective strategies for restoring proper microbiome composition with changes in CD4+ T cell counts in HIV patients is repeated FMT using capsulized stools. Furthermore, microbial metabolites, particularly SCFAs are short-chain fatty acids that commensal microorganisms create, play an important part in regulating immune homeostasis and modulating inflammatory pathways, thereby influencing disease progression and treatment outcomes. The two-way relationship between microbiota and the host immune system underscores the possibility of using the microbiome as a therapeutic target for optimizing immune reconstitution in HIV/AIDS. The goal of future studies should be to clarify the mechanistic pathways connecting gut dysbiosis to immune dysfunction in HIV/AIDS pathogenesis, thereby informing personalized microbiota-targeted interventions aimed at improving long-term immune outcomes and reducing the burden of comorbidities associated with chronic HIV infection.

5. Nutritional and Therapeutic Interventions

Nutritional and therapeutic interventions aimed at modulating gut microbiota composition. Interest in the intestinal microbiome has grown significantly due to its potential impact on immune system regulation and overall health outcomes. This section explores how dietary components, probiotics, prebiotics, and other treatments may influence gut microbiota composition and its activity, thereby impacting immune responses and disease susceptibility. Understanding the mechanistic interactions between these interventions and the development of targeted tactics depends on the microbiota to enhance immune function, reduce inflammatory conditions, and potentially prevent or manage various diseases.

5.1. Diet and Microbiota

The relationship between diet and the composition of the gut microbiota is crucial in shaping immune reactions and influencing inflammatory diseases. Current research, including that conducted by Gill et al. [35] and Sarkar et al. [36], highlights how dietary habits have a significant impact on the variety and function of the microbiota. Gill et al. highlight that high-fat, low-fiber diets characteristic of modern lifestyles tend to promote dysbiosis, characterized by reduced microbial diversity and altered metabolic activities, thereby fostering a pro-inflammatory milieu conducive to chronic inflammatory diseases. Conversely, traditional diets rich in fiber and diverse plant-based nutrients promote the growth of beneficial microbiota, such as butyrate-producing bacteria, which are essential for preserving the integrity of the intestinal barrier and regulating immunological responses [37, 38]. Sarkar et al. [36] further emphasize that early dietary exposures during critical developmental windows significantly influence long-term microbiota composition and immune health outcomes. They suggest that disruptions in early-life dietary patterns, including formula feeding versus breastfeeding and the timing of introduction to solid foods, can lead to dysbiosis and predispose individuals to inflammatory conditions later in life. Moreover, dietary components directly impact the production of microbial metabolites, like short-chain fatty acids which are essential for controlling inflammation and immunological regulation. It is crucial to comprehend the complex interactions that exist between immune function, gut microbiota, and food for devising effective dietary interventions to manage and prevent inflammatory diseases. Strategies aimed at promoting a diverse and balanced microbiota through dietary modifications, supplementation with prebiotics or probiotics, and targeted nutritional therapies hold promise in mitigating inflammation and improving overall health outcomes. Moving forward, integrating findings from dietary interventions in both experimental models and human studies will be critical in translating microbiota-focused dietary recommendations into clinical practice for personalized therapeutic approaches.

5.2. Vitamin D3 Supplementation

Vitamin D3, a fat-soluble secosteroid hormone, exerts profound effects beyond its classical role in calcium and phosphate homeostasis, especially in immune system modulation and gut microbiome. The research carried out by Charoenngam et al. [39] explores the close association between vitamin D3 supplementation and the composition of the microbiota. This research underscores vitamin D3's ability to influence microbiota composition and its activity within the gastrointestinal tract, implying possible ramifications for immune regulation and the pathophysiology of disease. In their investigation, Charoenngam et al. [39] observe that vitamin D3 levels correlate positively with the abundance of specific commensal bacteria crucial for gut homeostasis. Notably, *Bifidobacterium* and *Lactobacillus* species, acknowledged for their immunomodulatory properties and ability to generate short-chain fatty acids (SCFAs), exhibit increased colonization when vitamin D3 levels are high. These bacteria contribute to gut barrier integrity, regulate local immune responses, and participate in metabolic processes that influence host health. Furthermore, vitamin D3 supplementation appears to exert dose-dependent effects on gut microbial communities. Higher doses of vitamin D3 are associated with shifts in microbial composition towards a profile linked with reduced inflammation and improved metabolic outcomes. This modulation is attributed to vitamin D3's ability to enhance the expression of antimicrobial peptides (AMPs) and maintain epithelial barrier integrity, thereby promoting a symbiotic relationship between the host and microbiota.

The mechanistic insights gleaned from Charoenngam et al. [39] findings suggest that vitamin D3 acts through multiple pathways to influence gut microbiota dynamics. Beyond its direct effects on bacterial colonization and metabolism, innate and adaptive immunological responses that influence the gut environment are regulated by vi-

tamin D3. This multifaceted role underscores the potential of vitamin D3 supplementation not only in maintaining gut microbial diversity but also in reducing conditions linked to dysbiosis, like metabolic syndromes and inflammatory bowel illnesses (IBD). Going forward, more studies are necessary to clarify the exact chemical processes behind the effects of vitamin D3 on gut microbiota composition and its functional implications for human health. Such insights hold promise for the development of personalized nutritional strategies aimed at optimizing gut microbiota-mediated immune regulation and disease prevention. As vitamin D3 continues to emerge as a pivotal factor in gut health, integrating these scientific advancements into clinical practice could pave the way for innovative approaches to enhance gastrointestinal resilience and overall well-being.

5.3. The Effect of Macronutrients on Microbiota Composition

Diet is also an important factor influencing the composition and diversity of the microbiota. Short-term and long-term changes in diet lead to significant changes in the composition and diversity of the microbiota [40]. Dietary changes can be examined in terms of macronutrient composition and other dietary components. Macronutrients: The macronutrient composition of the diet influences the composition of the gut microflora. Dietary fats strongly influence the composition and function of the gut microbiota. A diet high in saturated fat and low in fiber decreases Bacteroidetes and increases *Firmicutes* and *Proteobacteria* [41–43]. Increased body fat percentage is associated with high dietary fat and *Lactococcus* and *Allobaculum* species [44]. Previous studies have shown that consuming a high-fat or low-fat diet with the same energy intake leads to several changes in the gut microbiota and metabolic profile of individuals. A low-fat diet is associated with an increase in *Blautia* and *Faecalibacterium* species, while a high-fat diet is associated with an increase in *Alistipes* and *Bacteroides* and a decrease in *Faecalibacterium*, which causes metabolic disorders and increases in inflammatory factors in the body. While low-fat diets have often been associated with improved plasma lipid levels, weight loss, and reduced inflammatory factors [45,46], studies have shown that consumption of polyunsaturated fatty acids such as omega-3 leads to an increase in butyrate-producing bacteria and has anti-inflammatory and anticancer effects [47,48]. The effects of dietary fats have not been adequately studied, but in general, beneficial fats such as omega-3 fatty acids or short-chain fatty acids (found in some dairy products) appear to have more beneficial effects on the type and composition of the gut microbiota, leading to better health by producing more butyrate and reducing inflammatory factors, while saturated fats or omega-6 fatty acids are associated with increased inflammation and disease. However, more studies are needed to clarify this issue.

5.4. Metabolites: The Diet-Microbiota Connection

The microbiota produces various metabolites as a result of food fermentation processes and thus affects the metabolism of the human body. Different metabolites have different effects on the body's metabolism and homeostasis control systems, and therefore the same diet has different effects due to the different microbiota residing in the intestine and, as a result, different metabolites. Metabolites are the connecting link between the microbiota and the diet. The most abundant metabolites produced by the fermentation of soluble fibers, including pectin and oligosaccharides, are short-chain fatty acids [49]. Short-chain fatty acids, through specific mechanisms and receptors, induce the production of some digestive hormones and affect appetite, digestion, and absorption of nutrients. Most short-chain fatty acids are produced by the fermentation of indigestible carbohydrates by the digestive enzymes of the human intestine, but fermentation of proteins secreted from the intestinal mucosa and compounds resulting from the digestion of dietary proteins can also produce these short-chain fatty acids [50].

5.5. Physical Exercises, Stress and Microbiota

Recent studies suggest that the microbiome may play a role in shaping exercise performance [51–53]. A growing body of evidence supports the idea that consistent physical activity and sports can impact both the composition and abundance of microbiota, providing overall benefits to the host, including enhanced immune defense and metabolic improvements [54–56]. The modulation of microbiome composition with exercise is possible in older adults, too. Exercise can impact the composition and diversity of microbiota, with potential benefits for human health and immune function [57]. Recent studies revealed that stress may modulate microbiome composition directly damaging the ecology of the intestinal microbial community. Further understanding the effect of microbial alteration on the immune system after stress might pave the way for new treatment strategies [58].

6. Discussions

To provide a thorough analysis incorporating results from multiple investigations on the influence of gut bacteria on immune system modulation, it's essential to synthesize and compare the strengths and weaknesses of the reviewed literature. This discussion will explore potential biomarkers, therapeutic implications, and limitations of current observational studies, contextualizing the findings within the broader research landscape.

6.1. Integration of Findings

The reviewed studies collectively underscore the microbiota's crucial function in regulating immune responses across various health conditions. Sanchis-Artero et al. [20] demonstrated that anti-TNFα treatment in Crohn's disease leads to significant changes in microbiota composition, suggesting potential biomarkers like *Faecalibacterium prausnitzii* to predict treatment response. Similarly, Fuentes et al. [23] highlighted altered microbiota compositions related to greater vulnerability to respiratory infections in the aging population, emphasizing the role of microbiota as potential biomarkers for disease risk. Rizzetto et al. [24] and Ge et al. [27] discussed dysbiosis-induced chronic inflammation and immune dysregulation in autoimmune diseases and cancer, respectively, revealing microbial interventions as novel therapeutic avenues. Early-life studies by Francino [11] and Martin et al. [12] elucidated how microbial exposures in infancy influence long-term immune health, advocating for strategies like probiotics to enhance immune resilience early in life.

6.2. Implications for Microbiota on Immune System Regulation

All of the data point to the gut microbiota's dual function in immune modulation, both as contributors to homeostasis and instigators of dysregulation in disease states. Round and Mazmanian [17] and Hrncir et al. [18] highlighted the microbiota's influence on immune system maturation, emphasizing the need for balanced microbial communities to foster optimal immune responses. However, H.J. Wu and E. Wu [8] cautioned that dysbiosis resulting from environmental factors could predispose individuals to autoimmune disorders, necessitating targeted therapies to restore microbial balance.

6.3. Potential Biomarkers and Therapeutic Strategies

The identification of microbiota-based biomarkers such as specific bacterial taxa or metabolites holds promise for predicting disease outcomes and tailoring therapeutic interventions. Spencer, Fragiadakis and Sonnenburg [59] proposed microbiota-targeted therapies to recalibrate immune responses in chronic diseases, suggesting a shift towards personalized medicine based on microbial profiling. Furthermore, research by Clemente, Manasson and Scher [31] and Gill et al. [35] highlighted dietary influences on microbiota composition, indicating potential therapeutic avenues through dietary modifications to mitigate inflammation and support gut health.

The **Table 1** synthesizes key findings from various studies, highlighting potential microbiota-based biomarkers and their implications for clinical applications. Each biomarker listed, like the *Faecalibacterium prausnitzii / Escherichia coli* ratio for Crohn's Disease or *Ruminococcus torques* in respiratory infections, demonstrates its specific association with disease conditions and predictive value for clinical outcomes. These biomarkers reflect the diverse roles of the intestinal microbiome in influencing immune reactions and disease states, underscoring their power as diagnostic or prognostic tools in personalized medicine. The references provided offer robust support, illustrating the depth of research into microbiota-driven biomarkers and their relevance in understanding and managing various health conditions effectively. This table serves to consolidate current knowledge and guide future research directions aimed at harnessing microbiota insights for improving healthcare strategies.

Table 2 provides a comparative overview of various therapeutic strategies discussed in the literature for modulating immune responses through gut microbiota manipulation. Some microorganisms like *Lactobacilli*, called "old friends", have become part of the human microbiota for hundreds of years, unfortunately we are losing our "old friends" recently [30]. *Lactobacillus rhamnosus GG (LGG)* may protect from the *Salmonella* species due to its lectin-like protein [31]. Probiotics and prebiotics focus on altering microbiota composition and promoting beneficial microbial growth, with probiotics showing potential in immune regulation despite mixed clinical outcomes. Dietary interventions, including specific diets or supplements, have demonstrated significant impacts on the immune system through modulation of microbiota diversity and inflammatory responses, albeit with considerations

for nutritional balance. Fermented food could be useful in combating the increased inflammation and diminished variety of microbiomes that are common nowadays [32]. The results show that it is feasible to modify the gut microbiota by Mediterranean diet intervention which may lead to a healthy aging process [33]. The fecal abundance of microorganisms thought to control the immunological response decreased after following a low-FODMAP diet (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols) [34]. By reducing adipose tissue inflammation, which may be mediated by changes in gut microbiota composition, curcumin has protective metabolic benefits in dietary Obesity-O-glucuronide [35]. Fecal microbiota transplantation (FMT) emerges as highly effective in restoring microbial balance in conditions like C. difficile infection, highlighting its potential but also the need for careful consideration due to infection transmission risks. Possible side effects of FMT may appear in recipients [36]. Each strategy presents unique mechanisms and potential side effects that should be weighed against their therapeutic benefits in clinical practice.

Table 1. Proposed biomarkers for disease prediction.

Biomarker	Associated Disease/Condition	Predictive Value	Reference
Faecalibacterium prausnitzii / Escherichia coli ratio	Crohn's Disease	Potential predictor of therapeutic response	Sanchis-Artero et al. [20]
Ruminococcus torques	Respiratory Infections in the Elderly	Indicator of pro-inflammatory profiles	Fuentes et al. [23]
Butyrate-producing bacteria	Type 1 Diabetes	Linked to immune regulation and inflammation control	De Groot et al. [29]
Short-chain fatty acids (SCFA)	COVID-19	Correlates with disease severity and immune dysregulation	Yeoh et al. [32]

Table 2. Comparative therapeutic strategies.

Therapeutic Approach	Mechanism of Action	Efficacy in Modulating Immune Responses	Potential Side Effects
Probiotics	Introduction of beneficial live microorganisms	Variable, depending on strain specificity and host factors	Minor gastrointestinal discomfort in some cases
Prebiotics	Promotion of growth of beneficial gut microbiota	Indirect, supports growth of probiotic bacteria	Flatulence and bloating in some individuals
Dietary Interventions	Modulation of microbiota composition and function	Varies with diet type, can influence systemic inflammation	Depends on dietary changes, potential nutrient deficiencies
Fecal Microbiota Transplantation (FMT)	Transfer of healthy donor fecal microbiota to recipient	Very useful for recurrent Clostridium difficile infection	Potential risk of transmitting pathogens, long-term safety concerns

6.4. Limitations of Current Observational Studies

Despite significant insights, several limitations in current observational studies warrant consideration. The majority of reviewed studies used short-term longitudinal or cross-sectional designs, limiting causal inference regarding microbiota-immune interactions. Variability in study populations, methodologies, and confounding factors such as diet and medication use further complicates the interpretation and generalizability of findings. Moreover, the complexity of microbiota composition and its dynamic nature pose challenges in identifying universal biomarkers applicable across diverse populations and disease states.

6.5. Comparative Analysis

Comparing the strengths and weaknesses of these studies against our findings underscores the robustness of the evidence base. While some studies provide detailed mechanistic insights into microbiota-immune interactions [17, 18], others offer practical implications for clinical practice [31, 59]. This review consolidates these findings, emphasizing the need for longitudinal, mechanistic studies to elucidate causal relationships between microbiota alterations and immune outcomes across different diseases. In conclusion, while the examined research as a whole demonstrates how important gut microbiota is for immune system modulation, further research is warranted to address existing gaps and strengthen clinical applications. Integrating microbiota-based biomarkers into clinical practice and advancing personalized therapeutic strategies hold promise for improving immune health outcomes.

Addressing the limitations through rigorous study designs and standardized methodologies will be crucial for improving our comprehension and harnessing the therapeutic potential of the gut microbiota-immune axis.

7. Conclusions

In conclusion, this review comprehensively elucidates the complex connection between immune system regulation and gut microbiome across various health conditions. The synthesized findings underscore the profound impact of microbiota composition on immune responses, from influencing disease susceptibility and severity to potential therapeutic interventions. Key insights include the identification of microbiota-based biomarkers for predicting treatment outcomes and disease risks, highlighting the potential for personalized medicine approaches. However, the present studies' limitations, such as study design variability and the complex nature of microbiota dynamics, necessitate further mechanistic research to validate causal relationships and optimize clinical applications. Moving forward, integrating microbiota-targeted therapies and dietary interventions tailored to individual microbial profiles holds promise for mitigating immune dysregulation and improving overall health outcomes.

Author Contributions

T.K.T. and A.R.: Developed the concept, conducted the data analysis, wrote, and revised the first draft of the manuscript. H.A.R.A. and Z.K.: Developed the concept, contributed to the draft review, editing, and validation. R.J.K.A. and A.S.: Developed the concept and participated in language editing, and data analysis. All authors have read and agreed to the published version of the manuscript.

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The article is comprehensive in its consideration of ethical concepts. The ethics committee gave the study the all-clear.

Informed Consent Statement

Not applicable.

Data Availability Statement

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Conflicts of Interest

The authors declared no conflict of interest.

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