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Review Article

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The Dual Role of Microbiota as a Therapeutic Target in Lupus Nephritis

Ramesa Shafi Bhat

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Department of Biochemistry, Science College of King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Lupus nephritis, a severe manifestation of systemic lupus erythematosus (SLE), involves kidney inflammation driven by immune dysregulation. Emerging evidence highlights gut microbiota as a key factor in lupus nephritis pathogenesis, with dysbiosis contributing to inflammation, tissue damage, and disease progression. In lupus nephritis, alterations in the gut microbiome have been observed, including an increased abundance of pathogenic bacteria and a decrease in beneficial microbes. These imbalances can trigger immune system dysregulation, leading to inflammation, tissue damage, and worsening disease symptoms. Research has shown that the gut microbiota influences systemic inflammation and autoimmunity through mechanisms such as the modulation of immune cell activation, regulation of cytokine production, and interactions with the intestinal epithelial barrier. Thus, targeting the gut microbiota has gained attention as a potential therapeutic strategy for lupus nephritis. Fiber-rich foods support gut health and may reduce inflammation, offering protective benefits for kidney function. Therapeutic strategies targeting the microbiome, including probiotics, fecal microbiota transplantation, and dietary interventions, are gaining attention as potential treatments. Probiotics may restore microbial balance, enhance intestinal barrier function, and modulate immune responses to alleviate lupus nephritis symptoms. Fecal microbiota transplantation, while promising in animal models, requires further investigation in humans. Targeting the microbiota represents a promising therapeutic approach for lupus nephritis, and ongoing research may lead to microbiota-based therapies as a crucial component of lupus nephritis management.

Keywords: Lupus nephritis, inflammation, microbiome, leaky gut

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INTRODUCTION

Autoimmune diseases are characterized by an extreme immune response, high inflammation, and the accumulation of immune complexes in tissues and organs, affecting approximately 6-8% of the global population.[1] These diseases are marked by immune system abnormalities that lead to inappropriate reactions of B and T cells against body tissues.[2] The etiology of these chronic and systemic conditions is complex and involves immunological dysregulation, genetic factors, and environmental influences such as diet, lifestyle, medication, and gut microbiota.[3] Most of the time, the exact triggers for the immune system's response to self-molecules remain unclear. These disorders can affect virtually any organ system and can occur in individuals of all ages, though they are significantly more common in women.[4] While certain underlying mechanisms link these conditions, the clinical presentations can be highly diverse. Symptoms can range from acute and life-threatening organ failure to subtle laboratory changes that might go unnoticed. Autoimmune diseases can be classified as a diverse group of disorders where the immune system attacks the body's own tissues, ranging from organ-specific conditions (e.g., Hashimoto's thyroiditis, type 1

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diabetes) to systemic diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS). While these conditions share common features such as immune dysregulation and inflammation, they have distinct pathophysiological mechanisms, with varying immune cell involvement and organ targets.[5] The role of gut microbiota in autoimmune diseases is increasingly recognized, particularly in SLE and lupus nephritis, where it may influence immune responses and disease progression. However, the significance of gut microbiota in other autoimmune diseases depends on their specific underlying mechanisms. Despite advances in diagnostic techniques and treatment options, early detection and targeted therapies for autoimmune diseases remain significant challenges.[6] Autoimmune diseases not only profoundly affect individuals and their families but also pose significant challenges for society and healthcare costs. The prevalence of autoimmune diseases is rising significantly in various regions worldwide, likely due to changes in environmental exposures, including significant shifts in diet, exposure to xenobiotics, air pollution, infections, lifestyle choices, stress, and climate change.[6-7]

Systemic lupus erythematosus is a chronic autoimmune condition marked by inflammation and immune-related damage to various organ systems, including the mucocutaneous, musculoskeletal, hematologic, and kidney systems.[8] Around 3.4 million people globally have been diagnosed with SLE, which predominantly affects women, with a global prevalence ranging from 30 to 60 cases per 100 000 in the UK and the USA.[9,10] The pathogenesis of SLE involves genetic and environmental factors, such as viral infections, impaired apoptosis, and exposure to ultraviolet-B radiation. Regarding immune response, autoantibodies primarily target nuclear and cytoplasmic antigens.[11] Around 50% of patients with SLE develop kidney damage, presenting symptoms such as hematuria, proteinuria, edema, or reduced kidney function, a condition referred to as lupus nephritis.[12] It is a critical and serious manifestation of SLE associated with a high mortality rate.[13] "Lupus," derived from the Latin meaning "wolf," refers to the distinctive facial rash associated with SLE, which resembles a wolf's bite.[14] Lupus nephritis is characterized by immune dysregulation and kidney inflammation developed within 3-5 years after the onset of SLE. Approximately, 10% of individuals with lupus nephritis may progress to end-stage kidney disease (ESKD) within 5 years of diagnosis (Figure 1). Given the high morbidity associated with lupus nephritis, effective treatment is crucial in preventing progression to ESKD.[15] Traditional laboratory biomarkers used in the clinical evaluation of lupus nephritis include immune serology tests like anti-double-stranded (ds) DNA antibodies and complement levels, as well as kidney function indicators such as proteinuria (measured via 24-hour urinary protein excretion or the urine protein-to-creatinine ratio [uPCR]), urinary sediment analysis, and glomerular filtration rate (GFR). While these parameters are well-established, they have demonstrated limited ability to detect lupus nephritis flare-ups early and often lack sufficient sensitivity and specificity to distinguish between active disease and chronic kidney damage. This distinction is critical for guiding treatment decisions.

Recent research suggests that gut microbiota may play a key role in worsening lupus by promoting immune complex deposition, activating the complement system, and increasing macrophage infiltration, all of which contribute to kidney inflammation.[16] Conditions like "leaky gut" can allow harmful bacteria to enter the bloodstream and form immune complexes that accumulate in the kidneys.[17] The harmful microbial products, such as lipopolysaccharides (LPS), translocate into the bloodstream, triggering systemic inflammation. These products can activate the innate immune system, including toll-like receptors (TLRs), which in turn stimulate the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6. The imbalance in microbiota may also contribute to the generation of autoantibodies, such as anti-dsDNA, by influencing B-cell activation. This triggers a pro-inflammatory response mediated by lymphocytes and macrophages, resulting in kidney inflammation. There is growing evidence supporting the role of intestinal dysbiosis in the development of lupus. Recently, researchers have increasingly focused on the role of the gut microbiota in lupus nephritis as gut health is significantly affected. Individuals with lupus nephritis may experience gastrointestinal issues such as diarrhea, dysbiosis (an imbalance in gut microbiota), and abdominal pain. This dysbiosis can influence the activity and severity of the disease, as the gut is vital for immune regulation.[18] However, the relationship between gut microbiota and autoimmune diseases remains an evolving field. Some research has failed to establish a significant connection between microbiota imbalances and autoimmune disease onset or progression. Factors such as genetics, diet, and medication use can influence the findings related to

MAIN POINTS

- Emerging evidence highlights the gut microbiota as a key factor in lupus nephritis, with dysbiosis (microbial imbalance) contributing to inflammation, tissue damage, and disease progression.
- Patients with lupus nephritis often show an increased abundance of pathogenic bacteria and a decrease in beneficial microbes, which can trigger immune system dysregulation and worsen symptoms.
- The gut microbiota influences systemic inflammation and autoimmunity by modulating immune cell activation, cytokine production, and interactions with the intestinal barrier.
- Probiotics, FMT, and dietary interventions are being explored as potential treatments for lupus nephritis, aiming to restore microbial balance and reduce inflammation.
- While FMT shows promise in animal models, further investigation is needed in humans. Targeting the microbiota may become an important part of lupus nephritis management in the future.

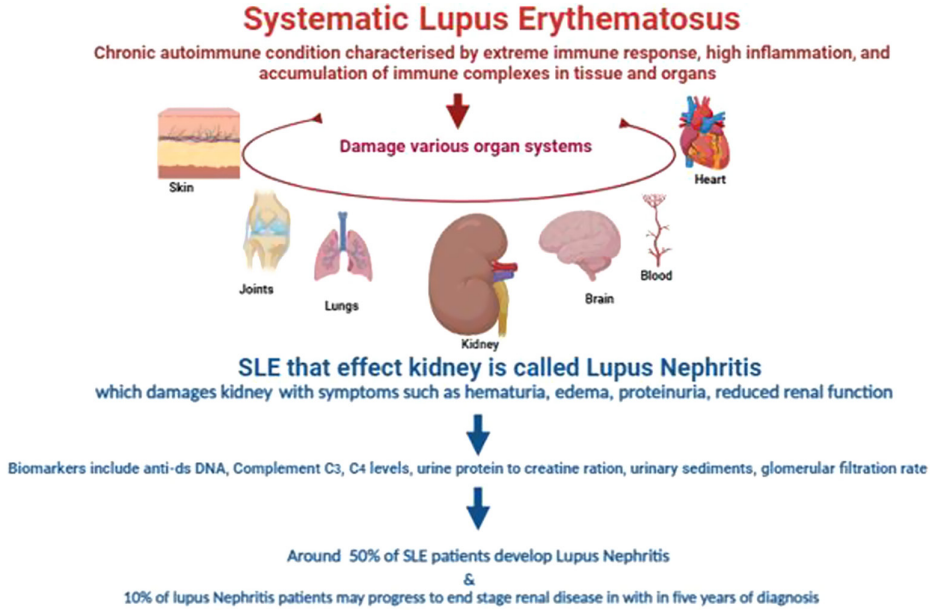

Figure 1. Systemic lupus erythematosus and lupus nephritis: organ involvement and kidney disease progression.

lupus nephritis. Genetic factors, such as immune-related gene polymorphisms, contribute to autoimmune disease susceptibility, while hormonal influences, particularly estrogen, play a key role in the higher prevalence of lupus in women. Epigenetic changes, like DNA methylation and histone modifications, can affect gene expression and contribute to immune dysfunction. A thorough understanding of lupus nephritis requires considering the interplay of these factors alongside the gut microbiota, as they collectively impact disease onset and progression. The microbiomes, predominantly bacteria, and their microbial products play a crucial role in regulating the development and function of the immune system in the human body. These microorganisms inhabit various sites, including the gut, skin, vagina, and oral cavity.[19] Types and abundance of microbes can vary between different organs and among individuals. Factors such as diet, environmental conditions, host genetics, and mode of delivery contribute to this wide microbial diversity.[20] A complex interaction between the host immune system and commensal microbiota is essential for maintaining gut homeostasis. In this symbiotic relationship, the microbiota aids in carbohydrate fermentation and digestion, vitamin synthesis, and the development of gut-associated lymphoid tissue while also preventing the colonization of harmful pathogens. In return, the host provides a suitable environment and nutrients for the survival of these microbes.[21] However, when this mutually beneficial relationship is disrupted and the interaction between immune cells and bacteria, the gut microbiota triggers autoimmune disorders. Researchers are working to clarify the microbiota's role in discovering new therapeutic strategies to maintain immune balance and homeostasis in SLE.[22] Probiotics are live microorganisms that provide a health benefit to the host when administered in sufficient quantities. Probiotics can influence systemic immune responses, maintain the balance of healthy microbiota in the intestinal mucosa, and potentially serve as adjunctive therapy for immune-mediated diseases.[23] The proposed mechanisms for these effects include promoting mucus secretion, producing antimicrobial peptides, supporting the integrity of the gastrointestinal epithelial barrier, facilitating interactions between gut microbiota and mucosal immune cells, and aiding the host immune system in response to harmful pathogens.[24] Despite these associations, the causes of gut microbiota imbalances and the pathways leading to lupus nephritis flares remain poorly understood. This review emphasizes the role of the gut microbiota in developing lupus nephritis, clarifying the regulatory mechanisms that affect inflammation and autoimmunity. While factors such as genetic predisposition, hormonal influences, and epigenetic modifications contribute to disease progression, the focus of this review will be specifically on the gut microbiota. Furthermore, it aims to detect probiotics as targeted treatment strategies for lupus. Therapeutic approaches that regulate gut microbiota composition to enhance or complement existing treatments for lupus nephritis are also discussed.

Altered Gut Microbiota in Lupus Nephritis

Gut microbiota interact with the immune system and play a crucial role in developing SLE.[25] Although, these microbiotas have the potential to serve as diagnostic and prognostic biomarkers, paving the way for new therapeutic strategies, the clinical utility remains uncertain as microbiome-based diagnostics are not widely used due to variability in microbiome data and the high cost of sequencing. Also, specific microbial compositions unique to lupus nephritis remain to be fully identified. It's important to note that gut microbiota composition can vary significantly based on factors such as diet, geography, genetics, and medication use. Thus, certain microbial profiles linked to

lupus nephritis might not be universally applicable across all populations. The variation in study methodologies, including differences in sequencing techniques, sample sizes, and patient selection criteria, can also lead to inconsistent results, making it challenging to compare findings across studies.

Biomarkers within gut microbiota may correlate with disease activity in such patients and could act as indicators for monitoring disease. Numerous studies have revealed significant changes in gut microbiota among lupus patients compared to healthy individuals.[15] *Bacteroidetes* and *Firmicutes* are the primary components of the human gut microbiota, yet a notable decrease in the *Firmicutes/Bacteroidetes* (F/B) ratio has been observed in lupus patients across various countries.[26] However, it should be noted that shifts in the F/B ratio are not specific to lupus nephritis and have been observed in multiple diseases, which may limit the specificity of this ratio as a diagnostic or monitoring tool for lupus nephritis. Active lupus patients exhibit a significantly lower F/B ratio than those with inactive disease, depending on ethnic background, lifestyle, or disease stage. Additionally, the gut microbiota composition varies between lupus patients with depression and those without.[26] To assess disease severity in lupus nephritis, several biomarkers are commonly used, including the SLE Disease Activity Index (SLEDAI), anti-dsDNA antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complement C3 levels. Research has also linked specific gut microbiota biomarkers to disease activity in lupus nephritis. For example, circulating immunoglobilin G (IgG) antibodies to *Enterococcus gallinarum*, a gram-positive commensal gut bacterium, are elevated in lupus patients and significantly associated with higher levels of anti-ribosomal P (RP), anti-dsDNA, and anti-Sm (Smith antibodies) autoantibodies as described in Figure 2. *Ruminococcus gnavus*, a gram-positive anaerobic bacterium, is found to be 5 times more abundant in SLE patients, especially in those with lupus nephritis.[27] Anti-RP antibodies correlate positively with anti-dsDNA levels and SLEDAI scores while showing negative correlations with complement C3 and C4 levels. Patients with active nephritis, particularly those with Class III and IV, have the highest serum levels of anti-RP strain-specific antibodies. Furthermore, the abundance of genera such as *Acholeplasma*, *Capnocytophaga*, and *Leptotrichia* is negatively correlated with SLEDAI scores, while *Bacteroides*, *Ruminococcus*, and *Akkermansia* exhibit an inverse relationship with serum complement C3 levels. The genus *Streptococcus* has also been associated with lupus activity. Recent studies have shown that lupus nephritis patients exhibit an increased abundance of *Enterobacteriaceae* and *Enterococcaceae*, alongside a decreased abundance of *Ruminococcaceae* in their gut microbiota, confirming the presence of dysbiosis. Additionally, *Actinobacteria*, *Bacillales*, *Coprobacter*, and *Lachnospira* are inversely correlated with the risk of SLE, whereas *Bacilli*, *Eggerthella*, *and Lactobacillales* may serve as risk factors for the disease.[28]

Possible Onset of Lupus Nephritis via Diet versus Gut Microbiota

To regulate immune tolerance within the gut, dietary practices are vital for maintaining proper gut function. Metabolic profile can serve as a valuable indicator of microbial activity in lupus patients. Fiber, a non-digestible edible carbohydrate polymer, resists digestion and is fermented into short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate in the gut. Inadequate dietary fiber, leading to low levels of SCFAs, can cause inflammation and disrupt both innate and adaptive immunity. However, it is important to recognize that other factors, such as genetics, medications, and overall microbial

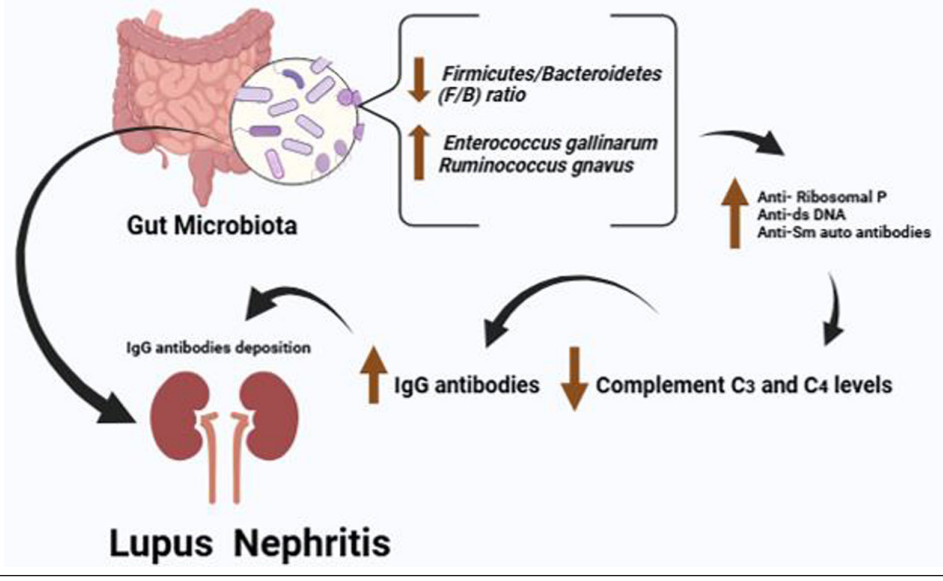

Figure 2. Gut microbial contribution to lupus pathogenesis: immunoglobilin G antibodies to gut pathobiont deposited in the kidney correlated with elevated anti-ribosomal P, anti-double stranded DNA, and anti-Sm autoantibodies.

diversity, also play crucial roles in shaping the microbiome and influencing disease progression. The relationship between fiber intake and inflammation contributes to alterations in gut microbiota that may promote the development of autoimmune disorders.[29] Short-chain fatty acids also serve as an energy source for gut microbiota, so changes in fiber intake can lead to reduced populations of gut microbes, a condition known as dysbiosis. This phenomenon is frequently observed in patients with lupus nephritis and can be partly attributed to insufficient dietary fiber intake.[30] While fiber and SCFAs are known to have beneficial effects on gut health and immune regulation, their precise role in the treatment of lupus nephritis remains uncertain. Patients with lupus nephritis often experience gastrointestinal issues, including bloating, diarrhea, or abdominal discomfort, which can complicate their ability to tolerate a high-fiber diet. These factors should be considered when evaluating dietary interventions as a potential treatment strategy for lupus nephritis. Therefore, while dietary fiber may offer benefits in terms of immune modulation and gut health, further clinical research is needed to establish its effectiveness and safety in the context of lupus nephritis treatment.

Short-chain fatty acids have several immunoregulatory functions, including anti-inflammatory effects and modulation of T cell activity through epigenetic pathways. Propionate is produced by *Bacteroides* and *Negativicutes* via the succinate pathway, acetate through the Wood-Ljungdahl pathway by *Blautia*, *Clostridium* spp., and *Streptococcus* spp., and butyrate is mainly generated by *Firmicutes* through the acetate CoA-transferase pathway. Adequate dietary fiber intake in lupus nephritis patients can help reduce disease activity by lowering serum levels of autoantibodies and inflammatory cytokines, as shown in Figure 3. Butyrate has been shown to alleviate kidney disease through G-protein-coupled receptor signaling and plays a critical role in maintaining gut homeostasis by activating PPAR-γ signaling. This activation suppresses the production of inducible nitric oxide synthase (iNOS) and prevents the overgrowth of nitrate-dependent microbes in the gut. Treatment with butyrate in lupus-prone mice has improved kidney damage by enhancing the *Firmicutes*-to-*Bacteroidetes* (F/B) ratio and increasing microbial diversity. Additionally, in NZB/W mice, histone deacetylase (HDAC) 6 inhibitors significantly reduced symptoms of lupus nephritis by inhibiting B-cell activation pathways. This evidence emphasizes the significant relationship between SCFAs and HDACs, suggesting that SCFAs may function as important immunomodulators in lupus nephritis. It is important to recognize that individual responses to these factors can differ significantly due to genetic, environmental,

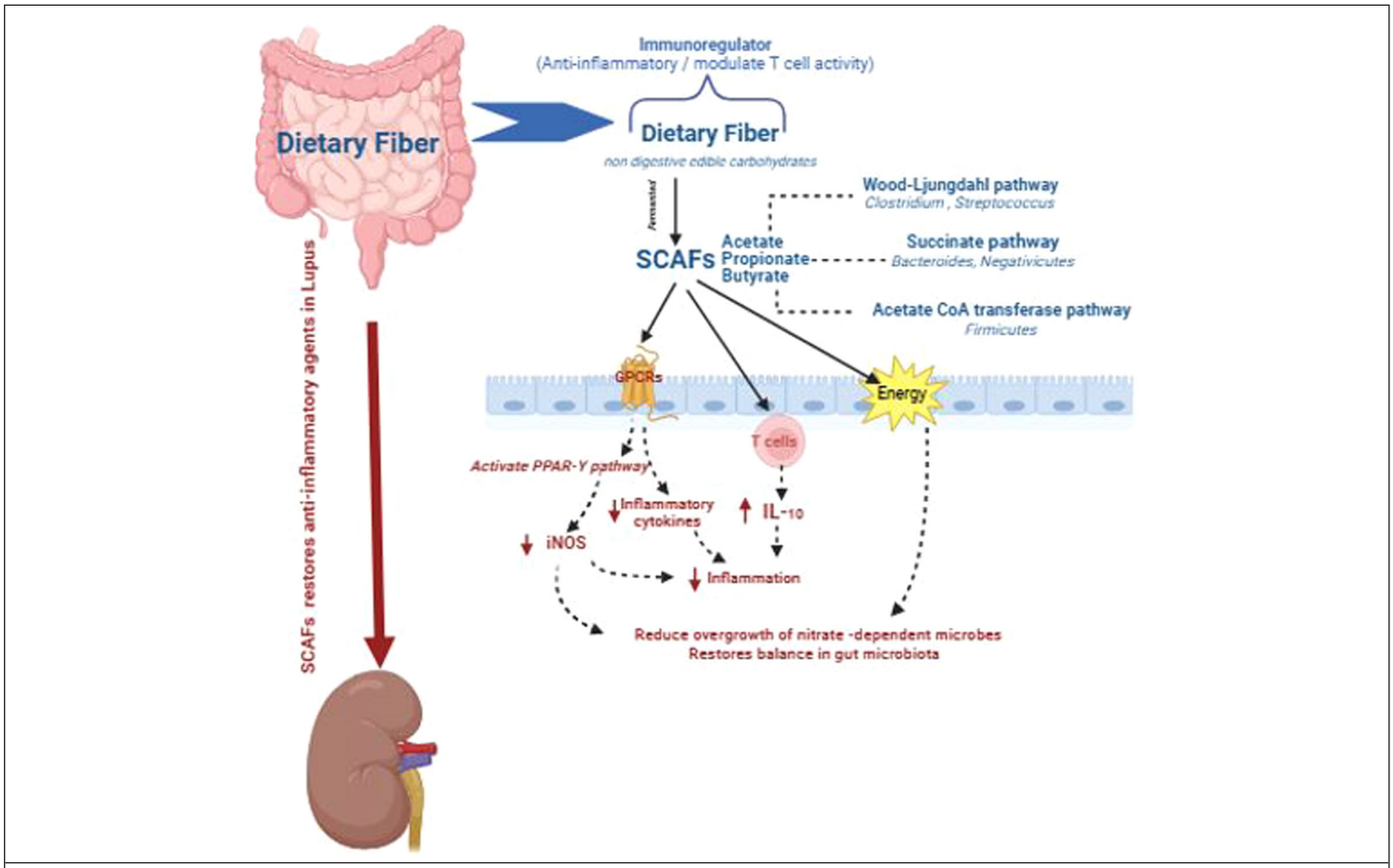

Figure 3. Dietary fibers as therapeutic agents for kidney inflammation by modulating the gut microbiome and restoring the balance between pro-inflammatory and anti-inflammatory factors in lupus nephritis patients.

and microbial variations. Additionally, understanding the interplay between regulatory pathways, such as cytokine signaling, immune cell activation, and other epigenetic mechanisms with HDACs and SCFAs, is critical for elucidating the pathogenesis of lupus nephritis and developing more targeted therapeutic strategies. Thus, microbial metabolites are crucial in the immune regulatory interactions between diet and gut microbiota. A low-fiber diet can promote immune dysregulation, leading to the deposition of immune complexes in kidney glomeruli. In contrast, lupus symptoms were significantly reduced in Lyn tyrosine kinase-deficient ($Lyn^{-/-}$) mice fed a high-fiber diet, indicating a potential link between high-fiber diets and immune modulation.[31] Few other dietary factors may also have significant effects on the gut microbiome and can influence disease progression in lupus nephritis. For example, high-fat diets have been shown to promote inflammation and alter gut microbiota composition, whereas certain micronutrients, such as vitamin D, play key roles in immune regulation.

Research on SLE rodent models indicates that resistant starch in the diet can suppress the growth of *Lactobacillus reuteri* by producing SCFAs, decreasing plasmacytoid dendritic cells (pDCs), and interferon pathways, thereby reducing lupus symptoms. This evidence suggests that resistant starch may inhibit the interferon pathway activated by gut pathobionts, which is particularly relevant to the pathogenesis of lupus nephritis. Elevated levels of fecal kynurenic acid, a metabolite derived from tryptophan, have been observed in some SLE patients, yet the exact role of tryptophan in lupus nephritis remains unclear. In certain rodent models of lupus nephritis, the gut microbiota has been shown to initiate immune responses through the degradation of tryptophan. A high-tryptophan diet has been associated with increased levels of *Lactobacillus* spp. and *Bacteroides dorei*, promoting pro-inflammatory effects. Conversely, a low-tryptophan diet has been found to improve lupus characteristics by regulating T-cell function and CD25 expression.[32] These effects are influenced by the broader dietary context, including factors such as protein intake, gut permeability, and host metabolism, all of which shape tryptophan metabolism and contribute to lupus nephritis pathogenesis. This highlights the need for a more comprehensive understanding of tryptophan's role in this condition. Rodent models are often used to investigate disease mechanisms because they provide insights into the pathophysiology. However, rodents differ from humans in various aspects, such as immune system function, metabolic pathways, and gut microbiome composition. For example, rodents typically have a simpler microbiome, which can lead to different interactions between the microbiota and host. Furthermore, differences in the genetic makeup and immune response mechanisms between species can limit the direct applicability of findings to humans. These models offer valuable preliminary data, but human studies are essential to establish more precise cause-and-effect relationships and to better understand how these interactions occur in human physiology. Similarly, diet-based interventions for lupus nephritis are still largely theoretical, and extensive research, especially in human studies, is needed to determine their practical applicability. Further clinical investigations are critical to evaluate the safety, efficacy, and feasibility of these interventions in real-world settings before specific dietary recommendations can be made for patients.

Microbial Imbalance Induced Leaky Gut in Lupus Nephritis

Modifying the host's microbiota and gut integrity could provide valuable insights for developing new treatments for lupus. The intestinal epithelium serves as the initial barrier against pathogens in the gastrointestinal tract. This epithelium comprises a single layer of various cell types essential for absorbing nutrients and water, defending against microbes, and modulating immune responses to sustain a balanced gut environment.[33] Tight junction (TJ) complexes formed between adjacent epithelial cells maintain the structural integrity of the gut barrier and regulate the passage of substances between cells. The functionality of TJs can be influenced by genetic and environmental factors, such as imbalances in gut microbiota and dietary elements.[33] Increased permeability in the gut barrier has been linked to the onset, advancement, and recurrence of lupus nephritis. Microbial imbalance in the gut can affect the gut barrier integrity through harmful bacterial growth and their byproducts, disrupting gut immune homeostasis. Research shows that restoring microbial balance can reduce gut permeability, highlighting the microbiota's crucial role in maintaining gut integrity. The presence of microbial components in the bloodstream of lupus patients indicates that microorganisms and their products may enter systemic circulation due to increased intestinal permeability.[34] Evidence from lupus patients with autoimmune hepatitis reveals the translocation of *E. gallinarum* into systemic organs, as bacterial DNA has been found in the liver. *E. gallinarum* can migrate from the gut to the liver, triggering the production of anti-dsDNA antibodies through TLR-7/8 activation in lupus patients, which is reversed by antibiotic treatment that inhibits the growth of *E. gallinarum* in tissues and eliminates pathogenic autoantibodies and T cells shown in Figure 4. TLR7 is primarily expressed on B cells and pDCs that produce type I interferons (IFNs), while TLR8 is predominantly found on monocytes, macrophages, and neutrophils. Activation of TLR7/8 triggers MyD88/IRAK/TRAF6 signaling pathways, leading to the activation of monocytes and B cells through nuclear factor (NF)-κB, or of pDCs through IRF7. Both TLR7- and TLR8-expressing cells are implicated in a variety of autoimmune diseases, with a particularly strong genetic association between TLR7 and lupus nephritis. Toll-like receptor 7 is also overexpressed in the peripheral blood mononuclear cells (PBMCs) of SLE patients. A negative correlation is found between *Synergistetes*, a phylum of anaerobic bacteria in the gut, and plasma anti-dsDNA antibodies and IL-6. Interleukin 6 is known to enhance the differentiation of T-helper (Th) 17 cells and increase the production of IL-17a, a key factor in driving autoimmunity in lupus.[35] Furthermore, various bacterial components have been identified in the blood of individuals with

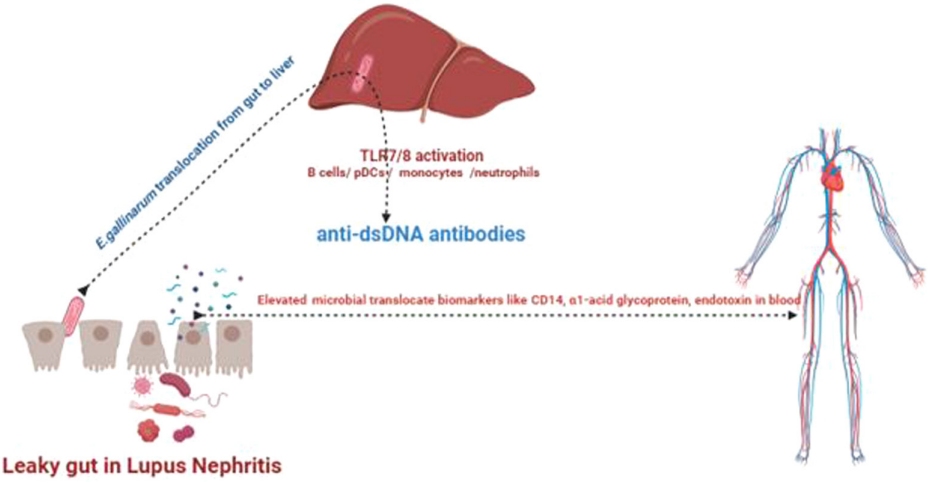

Figure 4. Microbial imbalance leads to leaky gut in lupus nephritis, compromising gut barrier integrity, which allows harmful bacterial growth and byproducts to pass through the intestinal wall, entering the liver and systemic circulation.

lupus nephritis, suggesting leakage from the gut. Elevated levels of biomarkers for microbial translocation, such as soluble CD14 and α1-acid glycoprotein, endotoxin from bacterial products, and fungal cell wall components have been detected in the serum of active lupus nephritis patients. However, there is limited understanding of the mechanisms behind losing gut barrier integrity in lupus nephritis. However, many rodent model studies provide clues about how dysbiosis could contribute to a leaky gut in lupus nephritis.

Certain bacteria can enhance gut integrity, suggesting that the development of a leaky gut may be linked to their absence. Microbial metabolites can enter the bloodstream through the gut epithelium, where they can influence immune activation and contribute to systemic autoimmunity. Toll-like receptor signaling in the intestine plays a crucial and distinct role in regulating commensal microbiota, triggering inflammatory responses, and balancing tolerance. The expression and interaction of TLRs, particularly TLR2, TLR6, TLR7, TLR8, and TLR9, play critical roles in the development of SLE. Pathogens typically contain ligands for various TLRs, activating multiple signaling pathways during infections or inflammatory conditions. Toll-like receptor expression can be localized to specific cell types and regions within the gut, with different TLR-induced cytokine responses, like TLR6 promoting the production of IL-10.[36] This complex regulation allows for precise adjustments in immune responses based on specific TLR interactions. Commensal microbiota can manipulate these levels through TLR ligands to facilitate colonization, enhance tolerance, and limit inflammatory diseases. Stimulation of intestinal epithelial cells with TLR-2 ligands prompted the redistribution of TJ proteins, which enhanced monolayer integrity. Toll-like receptor-2 is expressed in intestinal epithelial cells to recognize bacterial components and affect gut integrity. Lipoteichoic acid, a predominant surface glycolipid of gram-positive bacteria and a TLR2 ligand, increased mucin expression and reduced inflammation and gut leakage, suggesting beneficial bacteria's role in restoring gut barrier function. Toll-like receptor-7 is a disease-promoting factor, while TLR8 and TLR9 generally have more regulatory roles. Understanding these interactions is crucial for identifying therapeutic targets to modulate immune responses in lupus and other autoimmune diseases. Additionally, the relationship between TLRs and immune cells, such as ABCs, is important for disease pathogenesis. Since some TLRs, like TLR9, also have tolerogenic functions, such as establishing central B-cell tolerance, targeting them may help restore B-cell tolerance in autoimmune diseases. However, dual inhibitors targeting both TLR7 and TLR8 or TLR9 may be less effective than those focused solely on TLR7. Therefore, further research into the specific roles of each TLR is essential to refine therapeutic strategies. *Lactobacillus plantarum* enhances the expression of TJ proteins like ZO-1 and Occludin in humans.[37] When Caco-2 cell monolayers were exposed to *L. plantarum*, intestinal integrity improved by facilitating the translocation of ZO-1 to TJs.[37] However, blocking TLR2 with neutralizing antibodies negated this protective effect, indicating that *L. plantarum* likely activates TLR2 to confer its benefits. An anti-inflammatory molecule produced by *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* has been shown to restore gut barrier function and increase ZO-1 expression in rodents, suggesting its direct role in maintaining gut integrity. *Lactobacillus salivarius* restores barrier function in epithelial cell monolayers through the relocation of TJs to improve integrity. *Bacteroides fragilis* increased levels of SCFAs and IL-22, as well as the number of regulatory T cells, which likely contributed to enhanced TJ integrity and reduced inflammation.[38] The overgrowth of pathogenic *Bacteroides* and *Prevotellaceae_UGG-001* in experimental autoimmune rodents disturbs gut integrity, which can be improved by administrating broad-spectrum antibiotics. The commensal bacterium *Bacteroides fragilis* has been shown to decrease

colitis development. Enterotoxigenic *B. fragilis* showed increased intestinal permeability and damage to epithelial E-cadherin due to a metalloprotease toxin produced by *B. fragilis*, which degrades TJs in rodents. This highlights the importance of maintaining microbial balance for health. For example, *B. fragilis* can be beneficial in reducing colitis under normal conditions, but when it overgrows, it can disrupt gut integrity and potentially exacerbate disease outcomes. Similarly, *Clostridium difficile* produces toxins A and B, *Clostridium perfringens* produces enterotoxin, *E. coli* produces cytotoxic necrotizing factor 1, *Helicobacter pylori* produces vacuolating toxin, *Listeria monocytogenes* produces internalin, and *Vibrio cholerae* produces Zonula occludens toxin. Furthermore, *Pseudomonas fluorescens* can trigger zonulin secretion, which negatively regulates TJs, leading to changes in the cytoskeleton and disassembly. For instance, *B. fragilis* may act as beneficial in reducing colitis under normal conditions, but when overgrown, it can disrupt gut integrity and potentially worsen disease outcomes. This underscores the importance of microbial balance in maintaining health.

Additionally, infections with protozoans like *Giardia intestinalis* and *Blastocystis hominis* have increased rodent intestinal permeability. Rotavirus can also affect gut barrier function by altering the positioning of the TJ protein occludin. Thus, various microorganisms can either positively or negatively impact gut barrier integrity, and understanding their roles in the context of lupus may be crucial for restoring gut barrier function in patients.

The Potential Role of Microbiomes Beyond the Gut in Triggering Lupus

While the intestinal microbiome has been the primary focus of research, other microbial communities, such as those in the oral, skin, and genital tracts, may also exacerbate lupus nephritis. Imbalances in these microbiomes can influence immune responses, potentially triggering autoimmune reactions and disease flare-ups. Oral bacteria and their metabolites may interfere with genes related to autoimmune disease. Studies have shown a potential link between oral microbial DNA and nucleic acid sensing, suggesting that oral bacteria could influence systemic diseases, including lupus. The composition of the oral microbiome is highly variable, influenced by factors such as diet, smoking, poor oral hygiene, periodontitis, and salivary issues. The oral microbiota maintains a symbiotic relationship with the host in healthy individuals. However, an imbalance in the microbial population can lead to periodontal damage and increased systemic inflammation, which may contribute to the onset or worsening of Lupus nephritis symptoms. Oral mucosal lesions contribute to systemic disease exacerbation through autoantibody production triggered by oral microbial products in 5-40% of Lupus patients.[38] The oral microbiota of lupus patients differs significantly from that of healthy individuals, with an increased presence of species like *Fretibacterium, Prevotella,* and *Selenomonas.* Gum diseases such as Periodontitis also tends to develop earlier in lupus patients and is often worsened by co-existing infections. Elevated cytokine levels (especially IL-1β and IL-6) and inflammation in the oral mucosa of lupus patients suggest systemic cytokine responses by subgingival bacteria.[39] The microbiota of the genital tract, particularly in women, is dynamic and can influence autoimmune diseases. Changes in vaginal microbiota occur naturally due to hormonal fluctuations, sexual activity, and aging, with lupus nephritis development most frequent during reproductive years. Research on genital dysbiosis in lupus patients is still limited but shows that microbial imbalances in this area could contribute to disease progression. *Ureaplasma urealyticum*, the more prevalent pathogen found in active cases of lupus nephritis, is potentially linked to steroid use as the majority of patients are treated with prednisone.[40] Additionally, women with lupus have a higher risk of urinary tract infections, which can influence disease exacerbation. Active SLE patients with urinary tract infections had a distinct urinary microbiome compared to healthy individuals. The skin acts as a vital defense against pathogens, but in lupus, it is often compromised by skin lesions, which affect up to 80% of patients and can sometimes be the first visible symptom of the disease.[40] Studies have shown that the microbial composition of skin with lesions differs from that of unaffected skin in these patients. For example, *Pelagibacterium* and *Novosphingobium* are more abundant in lesioned areas, while *Curvibacter* is less prevalent. When comparing patients in remission with those experiencing active lupus, the presence of *Caulobacteraceae* was positively correlated with disease activity and negatively associated with complement C3 levels. In contrast, *Aerococcaceae* negatively correlated with disease activity and immunoglobulin G levels.[40] These findings suggest that the microbiota other than the gut play a role in modulating lupus activity, underscoring the need for further research into its contribution to disease development and progression.

Microbial Molecular Mimicry Triggers Lupus Nephritis

Molecular mimicry between bacterial antigens and self-components is implicated as a pivotal mechanism by which lupus nephritis is triggered.[41] This phenomenon occurs when molecular structures of microorganisms resemble the host's self-antigens, leading to an immune response that targets the body's tissues mainly by activating T and B cells. In the case of lupus, certain bacteria that share epitope sequences with self-antigens can trigger the production of cross-reactive autoantibodies. For instance, antigens from *Burkholderia* bacteria could bind to dsDNA antibodies in the serum of lupus patients, suggesting a link between *Burkholderia* molecular mimicry and the production of anti-dsDNA antibodies, a key marker of lupus nephritis.[41] Similarly, glycolipids from the mycobacterial cell wall could interact with anti-dsDNA autoantibodies in patients. These findings support the idea that bacterial infections may drive the formation of autoantibodies in lupus nephritis through molecular mimicry. The formation of anti-dsDNA antibodies is critical in the pathogenesis of lupus nephritis, as these antibodies are often found in higher concentrations in kidney

tissue compared to systemic circulation.[41] Their levels may also rise before lupus flares, making them a valuable diagnostic and monitoring tool for disease activity. Furthermore, recent research has shown that peptides from intestinal bacteria such as *Odoribacter splanchnicus* and *A. muciniphila* resemble the epitopes of self-antigens like the anti-Smith antigen and the Fas antigen. YLYDGRIFI peptide from the IS66 family of *O. splanchnicus* transproteases can influence the secretion of IL--γ and IL-17A from PBMCs in a subset of anti-Smith antibody-positive lupus patients due to the similarity between this bacterial peptide and the YLYDGRIFI autoepitope of human small nuclear ribonucleoprotein-associated proteins B and B', which are presented to T cells by the HLA-DR isotype. Additionally, the DGQFCM peptide from *A. muciniphila* is found at higher levels in lupus patients and shares similarities with the extracellular DGQFCG region of the human Fas ligand, potentially influencing its binding to IgG antibodies produced by memory B cells in patients. The HLA-DR3 allele is a key lupus susceptibility locus, and T cells play a central role in Lupus Nephritis development. T-cell epitopes on *Clostridium tetani* mimic human autoantigens, such as a DR3-restricted bacterial epitope (ABC247-261), and activate autoreactive T cells to induce autoantibody production, highlighting the potential of bacterial mimicry in triggering autoimmunity in DR3-susceptible individuals.[41] Similarly, the Ro60 antigen, associated with anti-Ro/SSA antibodies in lupus, shows cross-reactivity with Epstein–Barr virus nuclear antigen 1 (EBNA-1). Fecal samples from patients with active lupus promoted lymphocyte activation and the differentiation of naïve CD4+ cells into Th17 lymphocytes in vitro. An imbalance between Th17 cells and Tregs may contribute to the exacerbation of lupus nephritis, increasing antibody production and kidney deposition. Enriching patient stool samples with Treg-inducing bacteria, such as certain *Clostridia* strains, reduced the Th17/Th1 balance, and *Bifidobacterium bifidum* prevents excessive CD4+ lymphocyte activation.

Potential Therapy for Lupus Nephritis through Modulating Gut Microbiota

Modulating the gut microbiota as a treatment for lupus nephritis is still in its early stages, but its link to dysbiosis offers valuable insights for developing future therapeutic approaches. The therapeutic approaches, such as probiotics, prebiotics, dietary interventions, and microbiota transplants, show promise in promoting a healthy microbiota and restoring gut integrity. However, these approaches are still under investigation, and more research is needed to determine their efficacy and safety in lupus nephritis (Figure 5).

Probiotics as a Management Strategy for Lupus Nephritis through Restoring the Gut Flora

Probiotics are live microorganisms taken as supplements to promote the growth of beneficial bacteria, leading to positive health outcomes when consumed in appropriate amounts. Recent studies have highlighted several health benefits associated with probiotics. Probiotics may regulate gut microbial functions and impact metabolic processes in lupus nephritis patients. Specific strains, especially from the *Bifidobacteria* and *Lactobacillus* families, have shown promise in protecting against autoimmune diseases. Research indicates that the depletion of *Lactobacillus* and *Bifidobacterium* in the gut microbiota of rodent models with SLE suggests that bacterial supplementation with various *Lactobacillus* strains, known to benefit

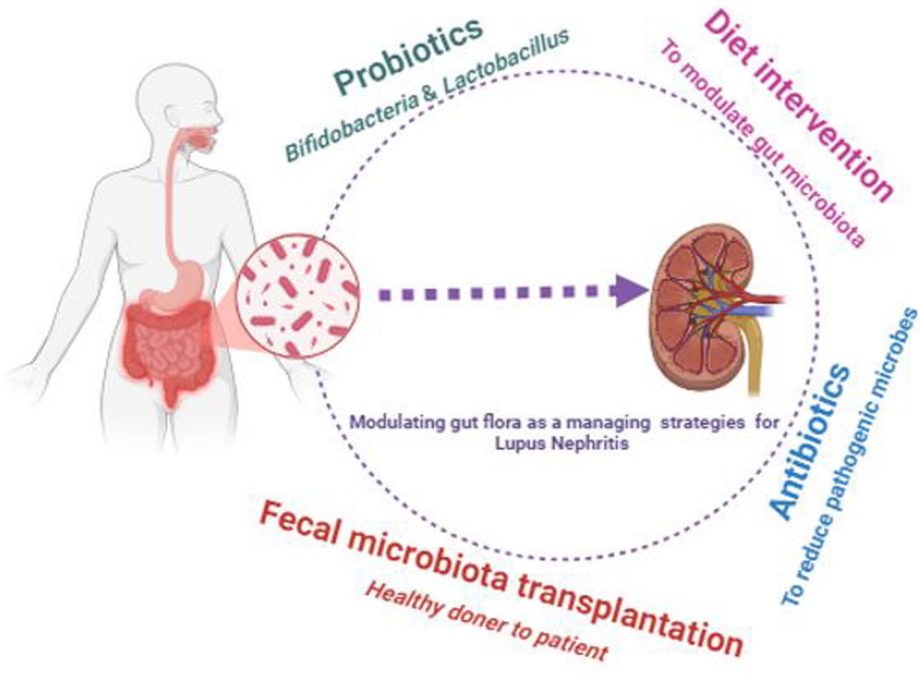

Figure 5. Approaches for modulating the gut microbiome in managing lupus nephritis.

other autoimmune conditions, might help alleviate symptoms in lupus patients. In rodent models, *Lactobacillus* spp. significantly reduced lupus nephritis and improved survival rates by lowering plasma levels of anti-dsDNA antibodies. Probiotic treatment is closely linked to lupus nephritis as it can regulate alterations in gut microbiota and metabolites. Studies have provided insights into the improvements in lupus nephritis patients and highlighted the potential of microecological therapies with probiotics as treatment options. Studies have focused on how bioactive synbiotic mixtures like dietary prebiotics enhance fecal microbiota, while probiotic supplementation increases intestinal hydrolytic enzymes and boosts immune function. Synbiotics can help restore lactobacilli populations, improve barrier function, and reduce colonic oxidative stress. Notably, synbiotic supplementation has decreased systemic inflammation and lupus disease activity while altering gut microbiota composition and function. Recently, Zhu et al.[42] investigated the impact of probiotics on gut microbiota and their metabolites in patients with new-onset lupus nephritis. The study found a reduction in pathogenic bacteria (such as *Prevotella*, *Bacteroides*, *and Enterobacteriaceae*) and an increase in beneficial bacteria (*Actinobacteria and Firmicutes*), leading to an overall rise in the *F/B* ratio. Probiotic treatment also influenced metabolic pathways, including amino acid biosynthesis and purine metabolism. Furthermore, bacterial taxa like *Negativicutes* and *Enterobacteriaceae* were identified as key predictors of treatment response. In healthy individuals, the gut microbiota and its metabolites are well-regulated, typically comprising about 20% *Bacteroides*, 80% *Firmicutes*, 1% *Proteobacteria*, and 3% other bacteria. *Firmicutes* and *Bacteroidetes* are the primary phyla involved in carbohydrate metabolism and the F/B ratio is a key indicator of gut flora balance. *Firmicutes* are the dominant phylum in the gut microbiome, primarily producing butyrate, an anti-inflammatory energy source for colonic epithelial cells. *Bacteroides* can also promote inflammation by secreting LPSs and toxic peptides. As the authors discussed above, lupus nephritis patients have significantly lower levels of *Firmicutes* compared to healthy individuals, while *Bacteroidetes* levels are increased, leading to a decreased F/B ratio. A rise in *Firmicutes* following probiotic treatment points to a potential anti-inflammatory effect. Probiotics can reduce the growth of pathogenic bacteria such as *Bacteroides*, *Prevotella*, *Faecalibacterium*, and *Parabacteroides* in the gut.[42] Probiotics also decreased the abundance of *Proteobacteria*. All *Proteobacteria* are gram-negative and primarily consist of LPSs, mainly pathogenic bacteria like *Escherichia coli* and *Salmonella.*[107] An increase in *Proteobacteria* has been reported in kidney disease, suggesting a pathogenic role for *Proteobacteria* in lupus nephritis.[42] LEfSe (linear discriminant analysis effect size) analysis identified 35 biomarkers in the lupus group before and after probiotic treatment. *Prevotellaceae* scored the highest followed by *Bacteroides.* ROC (Receiver-operating characteristic curve) analysis revealed that *Negativicutes* and *Enterobacteriaceae* are the strongest predictors in the lupus group during prebiotic treatment.[42] All these findings revealed that the composition of the intestinal flora and dysbiosis in lupus nephritis patients is implicated in the pathogenesis of this disease.

Probiotics as Immune Modulates in Lupus Nephritis

Lactobacillus Probiotics have the potential to modulate the immune system. Probiotics rapidly initiate anti-inflammatory responses by producing anti-inflammatory cytokines such as IL-4, IL-10, IL-11, and IL-13, while inhibiting pro-inflammatory cytokines like IL-1, IL-6, and TNF-α. This process involves regulatory T cells (Tregs) and T helper cells (Th cells). Notably, several strains, including *L. plantarum*, *Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus reuteri, Bifidobacterium longum*, and *Bifidobacterium breve*, have been identified as effective probiotics for addressing a range of symptoms in SLE. Probiotics induce immune shifts that decrease inflammation, alleviating lupus nephritis symptoms by modulating the numbers of Th17 and regulatory T (Treg) lymphocytes. For instance, oral administration of the probiotic *Lactobacillus delbrueckii subsp.* improved disease symptoms in a pristane-induced SLE mouse model by decreasing Th17 cell counts and the expression of IL-17a, a cytokine that promotes inflammation. Another probiotic, *Lactobacillus rhamnosus*, has been shown to influence the retinoic acid receptor-related orphan receptor gamma (RORγ), a transcription factor crucial for Th17 cell maturation, which may explain its role in reducing Th17 levels.[43] Both probiotics also decreased Th1 cell counts and the production of IFN-γ, a cytokine associated with inflammatory responses. *Lactobacillus reuteri* increased the expression of Treg lymphocytes and elevated levels of the transcription factor forkhead box P3 (FoxP3), essential for regulating pro-inflammatory lymphocytes and enhancing anti-inflammatory responses. Moreover, the probiotic treatment led to a reduction in pathogen-associated molecular pattern (PAMP) receptors like TLR-4, TLR-5, TLR-7, and TLR-9 in the liver, which are involved in the inflammatory process. *Lactobacillus paracasei* and *L. reuteri* were shown to decrease hepatic pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 by inhibiting the nuclear factor-kB (NF-κB) and mitogen-activated protein kinase signaling pathways.[44] Notably, *Lactobacillus paracasei* treatment also reduced left ventricular hypertrophy in the lupus model. Chronic consumption of *Lactobacillus fermentum* increased *Bifidobacterium* counts in the guts of female lupus nephritis mouse models, with symptoms including immune complex deposition in glomeruli, the presence of dsDNA autoantibodies, albuminuria, and notably, endothelial dysfunction and hypertension. *Lactobacillus fermentum* effectively reduced lupus disease activity and enhanced gut barrier integrity, leading to decreased plasma levels of LPSs, which in turn diminished immune activation by lowering T and B cell counts in the mesenteric lymph nodes (MLN) and reducing pro-inflammatory cytokines such as IL-17a, IFN-γ, TNF-α, and IL-21 in plasma. By preventing the development of the pro-inflammatory response, *L. fermentum* also prevented complications associated with SLE, including cardiac and kidney hypertrophy. *Lactobacillus fermentum* prevents high blood pressure

and improves endothelial function by reducing phosphorylation of endothelial nitric oxide synthase (eNOS) at the inhibitory site.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) involves transferring fecal bacteria from healthy donors into a patient's gut to restore microbial balance. This approach has gained attention as a potential treatment for autoimmune diseases, including SLE, due to its ability to address gut dysbiosis.[45] Microbiota-based therapies, including FMT, have gained increasing attention as potential novel treatments. FMT, in particular, is well-established for treating recurrent *C. difficile* infections and is emerging as a promising option for patients with inflammatory bowel disease and other autoimmune disorders. While the precise mechanisms behind the interaction between the gut microbiome and the host in autoimmune diseases remain unclear, FMT has demonstrated the ability to restore disrupted gut microbiota, rebuild the intestinal ecosystem, and modulate both innate and adaptive immune responses, leading to therapeutic benefits.[45] Studies in lupus animal models have demonstrated promising results with FMT as a therapeutic intervention. Although FMT has been studied in other autoimmune diseases, clinical trials investigating its use in lupus are still limited. Clinical trials of FMT for the treatment of SLE have been underway since 2020.[46] In a 12-week pilot study, 20 patients with active lupus received FMT as an adjunctive treatment. Over 3 consecutive weeks, patients were given encapsulated fecal microbiota. At the final evaluation, there was a notable reduction in SLE Disease Activity Index (SLEDAI-2K) scores and serum anti-dsDNA antibody levels, with no significant serious adverse events observed compared to baseline. The treatment also resulted in a significant increase in the abundance of bacteria that produce SCFAs and a decrease in bacteria associated with inflammation. The elevated SCFA levels in the gut led to reduced cytokine levels related to inflammation and a shift in the ratio of CD4+ memory cells to naive cells in peripheral blood. Single-cell analysis of peripheral blood post-treatment revealed a reduction in T cells and an increase in natural killer (NK) cells. Furthermore, subcluster analysis showed increased expression of IL7R and CD28 in CD4+ T cells and elevated granzyme H (GZMH) and NK cell granule protein 7 (NKG7) in CD8+ T cells. Additionally, there was a decrease in the expression of interferon-related genes in CD4+, CD8+, double-positive (DP), NK, and B cells.[47] Interestingly, patients who did not respond to FMT exhibited a higher abundance of interferon-related pathways. The study found that the efficacy of FMT was negatively associated with the expression of interferon-related genes in lymphocytes and myeloid cells. This preliminary trial offers promising evidence that FMT could be a safe and effective novel treatment for active SLE.

Antibiotic Therapy to Reduce Pathogenic Bacteria

The use of antibiotics in treating lupus is still controversial. Antibiotics can reduce pathogenic bacteria, enrich beneficial microbes, and improve gut permeability, which may slow disease progression. However, there are practical limitations in using antibiotics for lupus nephritis patients. Antibiotics may interfere with the therapeutic effects of prednisone, a commonly used medication for lupus. Furthermore, the overuse of antibiotics could lead to the development of antibiotic-resistant infections, which pose a significant risk, especially in patients who are already immunocompromised. [48] Therefore, more research is needed to refine antibiotic treatment strategies for lupus to target pathogenic bacteria without disrupting the gut microbiota balance. In recent years, various studies have explored the use of antibiotics as a potential treatment for lupus in mouse models. For example, treatment with broad-spectrum antibiotics or vancomycin in lupus-prone MRL/lpr mice, initiated after disease onset, has been shown to reduce harmful gut bacteria, promote the growth of beneficial probiotics, and restore intestinal barrier function, leading to improved lupus symptoms.[49] Additionally, antibiotic therapy has been found to correct the Treg/Th17 imbalance in these mice and mitigate hypertension caused by Th17 cell infiltration.[49] Similarly, vancomycin treatment in NZB/WF1 lupus mice led to the elimination of *E. gallinarum*, a gut pathogen, enhanced intestinal barrier integrity, and delayed lupus However, other studies have reported contradictory results. For instance, one study found that antibiotic treatment had no significant effect on the gut microbiota or the progression of SLE in NZB/WF1 mice, and the underlying mechanisms for this outcome remain unclear. Antibiotic treatment worsened the disease in MRL/lpr mice, potentially due to the short duration and insufficient dosage of antibiotics administered before disease onset. Moreover, while vancomycin therapy generally improved lupus symptoms in pregnant and postpartum MRL/lpr mice but worsened lupus in these mice, vancomycin treatment reduced Treg cell expression by inhibiting indoleamine 2,3-dioxygenase (IDO) and increased interferon-gamma (IFN-γ).[50]

CONCLUSION

Lupus nephritis represents a complex and growing global health challenge, affecting many individuals worldwide. This condition is characterized by dysregulated immune responses that lead to systemic inflammation, kidney damage, and significant morbidity. While genetic, environmental, and immunological factors all contribute to the development and progression of lupus nephritis, the emerging role of the gut microbiota offers new insights into its pathogenesis and potential therapeutic avenues. The gut microbiota plays a critical role in maintaining immune homeostasis, and disruptions in this balance may influence the onset and severity of lupus nephritis. Emerging evidence suggests that interventions aimed at restoring microbial balance, such as probiotics, prebiotics, FMT, and dietary changes, could modulate immune responses, reduce inflammation, and potentially slow disease progression. Long-term antibiotic use can disrupt the gut microbiota and lead to unintended consequences, including the development of antibiotic resistance and an increased risk of secondary infections.

Therefore, while antibiotics may offer short-term benefits in addressing microbial imbalances, the potential risks should be carefully considered. These risks highlight the need for more targeted therapeutic approaches that can balance microbial modulation with the preservation of gut health and immune function.

Despite these promising findings, much remains to be understood about the mechanisms linking the gut microbiota to lupus nephritis. Ongoing research is crucial for identifying specific microbial factors that may exacerbate disease progression and elucidating the pathways through which the microbiota influences immune dysregulation in lupus. Targeting the gut microbiota presents a promising therapeutic strategy for managing lupus nephritis. However, more work is needed to understand the underlying mechanisms fully and to translate these insights into effective microbiota-based treatments as part of a comprehensive approach to managing this disease.

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