Autoimmunity Reviews 24 (2025) 103921

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Systemic lupus erythematosus and the gut microbiome: To look forward is to look within – A systematic review and narrative synthesis

Daniel Guimarães de Oliveira [a,b,c,*], Alexandra Machado [d], Pedro Castro Lacerda [e], Zoe Karakikla-Mitsakou [f], Carlos Vasconcelos [a,g]

[a] Unit for Multidisciplinary Research in Biomedicine (UMIB), School of Medicine and Biomedical Sciences (ICBAS), University of Porto, Rua Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal
[b] i3S – Instituto de Investigação e Inovação em Saúde, University of Porto, Rua Alfredo Allen, 208, 4200-135 Porto, Portugal
[c] UDAI – Autoimmune Disease Unit, Internal Medicine Department, Unidade Local de Saúde do Tâmega e Sousa, Avenida do Hospital Padre Américo, 210, 4560-136, Guilhufe, Penafiel, Portugal
[d] Internal Medicine Department, Unidade Local de Saúde Entre Douro e Vouga, Rua Dr. Cândido de Pinho, 4520-211 Santa Maria da Feira, Portugal
[e] INSA – National Health Institute Dr. Ricardo Jorge, Rua Alexandre Herculano, 321, 4000-055 Porto, Portugal.
[f] Lupus Europe, Rue d'Egmont 11, 1000, Bruxelles, Belgium
[g] Unidade de Imunologia Clínica, ULS Santo António, Largo Prof. Abel Salazar, 4099-001, Porto, Portugal

ARTICLE INFO

Keywords:
Systemic lupus erythematosus
Gut microbiome
Dysbiosis
Fecal microbiota transplantation
Autoimmunity

ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease shaped by complex interactions involving genetic and environmental factors. Among these, the gut microbiome is emerging as potentially modulating immune responses and influencing disease susceptibility, progression, and activity.
Objectives: To synthesize current evidence on gut microbiome changes in adult SLE patients, framed along the clinical pathway – from diagnosis to treatment – to help bridge bench and bedside for microbiome-informed SLE care and research.
Methods: A systematic search identified primary research studies examining gut microbiota in adult SLE patients. Studies were reviewed in a stepwise manner by independent investigators. Findings were synthesized narratively, emphasizing human data.
Results: SLE patients exhibit gut microbiome dysbiosis, with reduced microbial richness and altered bacterial taxa. A lower *Firmicutes/Bacteroidetes* ratio is frequently observed. Enrichment of specific taxa, such as *Enterococcus*, *Lactobacillus,* and *Ruminococcus gnavus,* is reported. Dysbiosis correlates with increased gut permeability, immune activation, and autoreactivity. Clinical associations include disease activity, flares, nephritis, and other manifestations. SLE treatments, such as hydroxychloroquine and corticosteroids, influence the microbiome. Emerging interventions such as dietary modulation and fecal microbiota transplantation show promise in early studies. However, considerable heterogeneity exists across studies in terms of patient characteristics, methodology, and taxa-level findings.
Conclusions: The gut microbiome has multifaceted associations with SLE pathogenesis, disease activity, and therapeutic response. Translation will require standardized methods, functional validation, longitudinal follow-up, and clinical integration. While uncertainties remain, the gut microbiome is increasingly relevant, and clinicians caring for patients with SLE should be aware of its emerging implications.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, immune-mediated disease with a complex pathogenesis shaped by both genetic predisposition and environmental factors [1]. Over recent decades, the incidence of many autoimmune conditions has surged, with SLE incidence tripling over the past 50 years – a trend not fully explained by improvements in diagnosis [2]. Environmental pressures, such as

* Corresponding author at: Unit for Multidisciplinary Research in Biomedicine (UMIB), School of Medicine and Biomedical Sciences (ICBAS), University of Porto, Rua Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal.
E-mail address: daniel.gtro@gmail.com (D. Guimarães de Oliveira).

https://doi.org/10.1016/j.autrev.2025.103921
Received 11 April 2025; Received in revised form 30 July 2025; Accepted 25 August 2025
Available online 26 August 2025

dietary shifts, antibiotic overuse, and diminished constitutive microbial interactions, are thought to contribute to this increase by influencing the immune system [3].

A major route through which these factors exert their effects is the gut microbiome, a vast community of bacteria, viruses, fungi, protozoa, and archaea that co-evolves with the host and profoundly affects immune homeostasis [4,5]. Dysbiosis—alterations in the composition or function of these communities—disrupts this delicate balance, and growing evidence implicates such imbalances in the onset, progression, and management of autoimmune diseases, including SLE [6,7].

It has now been ten years since the seminal study by Hevia and colleagues (2014) [8] first reported gut microbiome dysbiosis in SLE patients, sparking a growing body of research into this connection. However, the clinical implications of these findings remain poorly defined. In this review, we synthesize current evidence on gut microbiome changes of adult SLE patients and frame this discussion through a clinical pathway lens – mirroring how a clinician encounters and manages SLE, from diagnosis through treatment.

This narrative review thus aims to make emerging microbiome research more accessible and actionable for SLE clinicians, while also promoting translational insights. By aligning both perspectives, we seek to inform both practice as well as future research toward microbiota-informed biomarkers and therapeutic strategies.

2. Methods

A search was carried out of Medline via PubMed, Scopus, and Scielo databases looking in the broadest terms for papers published until 31 December 2023 using relevant keywords and Medical Subject Headings (MeSH) terms: *((“lupus erythematosus, systemic” [MeSH] OR “systemic lupus erythematosus” OR “disseminated lupus erythematosus”) AND (microbiota [MeSH] OR “microbial community” OR “microbial composition” OR “microbial structure” OR microbiome))*.

Articles in languages other than Portuguese, English, French, Spanish, or Italian were excluded. Only observational or experimental studies that included the gut microbiome in adult patients were considered, with reviews kept for reference. Additional articles were added when relevant from consulting references or from the authors’ own bibliographic catalog.

The search was performed independently by three of the researchers (DGO, PCL, AM). Duplicate references were immediately excluded. Afterwards, papers were reviewed by DGO and PCL and included independently, according to the above criteria in a stepwise approach of title, abstract, and entire paper. Differences were discussed and resolved by a senior investigator (CV). The overall study identification and selection process is presented in Fig. 1, which follows the structure of a PRISMA flow diagram to ensure transparency and reproducibility.

From each selected study, we recorded the author, year, publication, country or region, study design, participant characteristics, and microbiota analysis methods. We then extracted key findings on the gut microbiome in SLE, focusing on specific bacterial or taxonomic differences between patient and control groups. Where applicable, we also noted any associations with disease activity or organ involvement. Relevant data points are combined and presented in Tables 1–5. Findings are summarized, qualified, and presented in narrative form. A list of included studies, along with their characteristics and main findings is provided in Supplemental Table 1.

3. Results

We identified 43 observational or experimental studies that directly assessed the gut microbiome of adult SLE patients, and were included in this review (Fig. 1).

Study sample sizes ranged from 8 to 117 participants, with an average of 32 SLE patients per study. Most studies ($n = 38$) included a healthy control group, while some ($n = 6$) also included patients with other diseases, such as Rheumatoid Arthritis (RA) (n = 3) and Sjögren’s Syndrome (SSj) (n = 3) (see Supplemental Table 1 for study-level

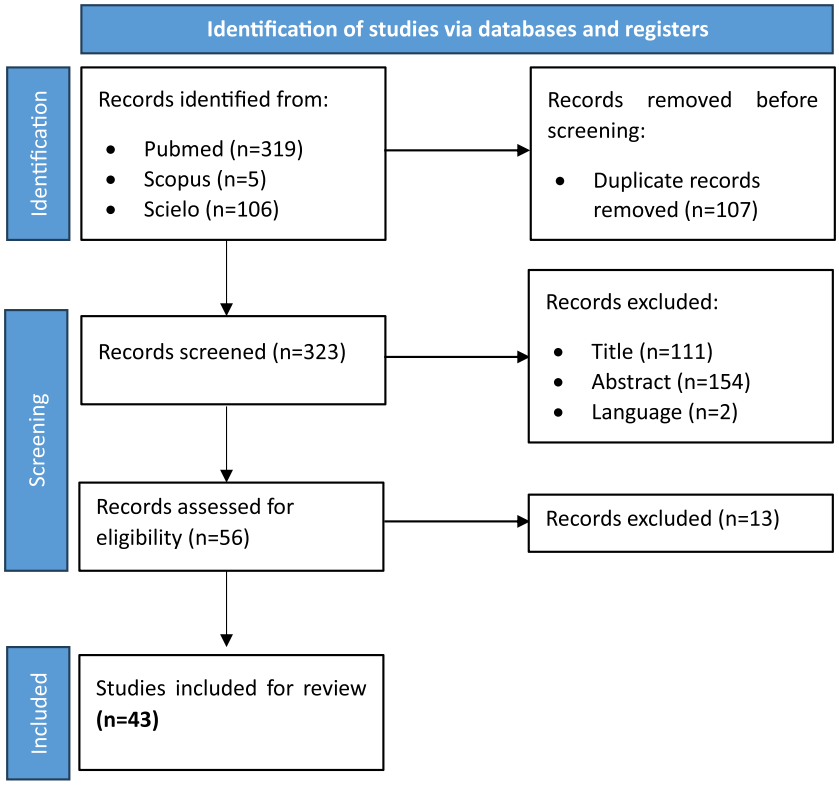

Fig. 1. Flowchart depicting systematic search, screening, inclusion, exclusion and review process for scientific journal articles on SLE and microbiome performed on Pubmed, Scopus and Scielo databases, up to 31 December 2023.

details). As expected, most of the patients were female, although 18 studies also included male participants. The average age of patients was 40.5 years. A wide range of exclusion criteria were applied, such as disease activity levels or specific drug use. Notably, only five studies reported conducting longitudinal assessments.

3.1. Dysbiosis in SLE: evidence for altered microbial composition and function

SLE is characterized by significant alterations in the gut microbiome, evidenced by changes to microbial diversity and community structure, compared with healthy controls (HC), as summarized in Tables 1 and 2. Metrics such as alpha and beta diversity, frequently used to assess microbiome health, underscore these alterations. *Alpha* diversity, which reflects how many different species (richness) and how evenly distributed they are (evenness) within individual samples [8], was generally reduced in SLE patients compared to healthy controls [9–12]. However, indices such as Shannon and Simpson, sensitive to the relative distribution of species, did not consistently show significant differences [13–17].

Beta diversity offers additional insights by comparing microbial community composition across groups [8]. Across the studies analysed, patients mostly displayed beta diversity similar to or higher than that of healthy controls, as indicated by Bray-Curtis or Unifrac distances [18–20].

Taxonomic markers such as the *Firmicutes/Bacteroidetes* (F/B) ratio further emphasize microbial imbalances in SLE. Broadly, the F/B ratio reflects the relative abundance of these two dominant gut phyla and has been proposed as a marker of gut homeostasis, although its interpretation varies by clinical context [21]. Across diverse populations, including Spain, Egypt, and China, a lower F/B ratio was consistently reported in SLE patients compared to healthy controls [10,13,22–26]. In untreated patients, this imbalance has shown diagnostic potential, accurately distinguishing SLE patients from controls in some studies [28]. However, this trend is not universal, with some studies reporting no significant difference [9,27,28] potentially due to methodological or population-level variability [29].

Shifts in the F/B ratio observed in SLE reflect uneven changes across genera. Within the *Bacteroidetes* phylum, increased levels of *Prevotella* have been reported in SLE [13]. Conversely, key genera within *Firmicutes*, such as *Faecalibacterium* [11,19,30,31], and *Roseburia* [11,16] were often depleted in SLE. Despite the general trend of reduced *Firmicutes* and increased *Bacteroidetes*, exceptions exist. For instance, *Lactobacillus* [9,17,28] and *Streptococcus* [9,14,20] within the *Firmicutes* phylum were enriched in SLE. Notably, *Lactobacillus* has even been proposed as a potential biomarker. This is supported by Ling et al. (2023), who also identified *Anaerococcus* and *Gardnerella* as additional predictive genera, with high diagnostic accuracy [17]. Table 2 presents how specific taxa associate with SLE compared with HC.

Adding to the complexity of these patterns, individual species can display varying effects depending on their context. This is particularly evident with *Bacteroides thetaiotaomicron,* which acts as an anti-inflammatory agent in innate immune cells [30], but emerges as a likely pathobiont in SLE [2] — a commensal microbe capable of promoting inflammation or disease under specific host or ecological/environmental conditions [31].

Multiple factors can influence microbial composition and function in SLE. One direct influence arises from the continuity of microbial ecosystems, such as the oral-gut axis. Van der Meulen demonstrated that oral microbiota could affect gut microbiota composition in SLE patients [11]. Chen et al. (2021) extended this observation through strain-level analysis, identifying *Actinomyces massiliensis,* and *Shuttleworthia satelles*—species linked to oral inflammation—enriched in the gut microbiota of SLE patients compared to healthy controls [32]. Whether these differences reflect inherent susceptibility to colonization or secondary effects of SLE remains unclear.

A key question remains: are microbiome changes in SLE patients pathological contributors or byproducts of the disease and its management? Rojo et al. (2015) proposed an intriguing perspective, showing that while the microbial composition of fecal samples from SLE patients and matched controls did not differ significantly, metabolomic analysis revealed substantial functional differences [33]. This suggests that conditions such as SLE alter not just host physiology but microbial metabolism as well, in ways that could potentially influence bacterial activity and signaling.

> *Thus, dysbiosis in SLE appears to be driven by genera-, species-, or even strain-specific effects that influence, but are also influenced, by the host* [12].

3.2. Mechanisms of microbiome influence on SLE

If indeed these microorganisms contribute to disease pathogenesis, there are several potential mechanisms through which they might do so.

3.2.1. Gut permeability and direct translocation

In healthy conditions, the intestinal barrier is a critical regulator of the interaction between endoluminal contents of the gut and systemic circulation. Damage to this barrier, resulting in increased permeability, can allow bacteria, microbial peptides, or metabolites to translocate

Table 1
Summary of alpha diversity and beta diversity findings in SLE (vs HC). Results present findings supported by more than one reference only.

	Taxon/Reference	[9]	[14]	[17]	[18]	[20]	[22]	[23]	[25]	[26]	[28]	[32]	[40]	[50]	[73]
Phylum	*Bacteroidota (Bacteroidetes)*						↑	↑	↑					↑	
	Firmicutes							↓	↓					↓	
	Mycoplasmatota (Tenericutes)	↓								↓					
	Pseudomonadota (Proteobacteria)		↑											↑	
Order	*Eubacteriales (Clostridiales)*							↓						↓	
Family	*Enterobacteriaceae*		↑											↑	
	Oscillospiraceae (Ruminococcaceae)		↓					↓			↓			↓	
Genus	*Dialister*												↓	↓	
	Faecalibacterium	↓		↓	↓										
	Lactobacillus	↑		↑											
	Prevotella													↑	
	Roseburia	↓	↓												
	Streptococcus	↑	↑			↑							↑		
Species	*Bacteroides fragilis*											↑			
	Faecalibacterium prausnitzii	↓													
	Streptococcus anginosus	↑			↑						↑				↑

↑ Higher in SLE or Lower in HC vs SLE..
↓ Lower in SLE or Higher in HC vs SLE..

Table 2
Summary of taxa associations with SLE (vs HC). Results present findings supported by more than one reference only.

	Taxon/Reference	[9]	[14]	[17]	[20]	[23]	[24]	[25]	[27]	[30]	[35]	[43]	[60]	[76]
Phylum	*Bacteroidota (Bacteroidetes)*					↑	↑	↑				↑		
	Firmicutes					↓	↓	↓				↓		
	Mycoplasmatota (Tenericutes)	↓							↓					
	Pseudomonadota (Proteobacteria)		↑									↑		
Order	*Eubacteriales (Clostridiales)*					↓						↓		
Family	*Enterobacteriaceae*		↑									↑		
	Oscillospiraceae (Ruminococcaceae)		↓			↓						↓		
Genus	*Blautia*									↑			↑	
	Dialister										↓	↓		
	Faecalibacterium	↓										↓		↓
	Lactobacillus	↑		↑						↑				
	Prevotella									↑		↑		
	Roseburia	↓	↓											
	Streptococcus	↑	↑		↑									
Species	*Bacteroides fragilis*										↑			
	Faecalibacterium prausnitzii	↓												
	Streptococcus anginosus	↑												↑

↑ Higher in SLE or Lower in HC vs SLE..
↓ Lower in SLE or Higher in HC vs SLE..

across the mucosa, triggering immune activation, inflammation and disease [34].

Fecal albumin, calprotectin and zonulin are often used as markers of gut barrier disruption [35] and all have been reported as increased in fecal samples from SLE patients [11,35,36]. Elevated plasma zonulin has also been observed [36]. Azzouz et al. (2019), showed not only increased IgA, but also IgG and IgM in fecal samples from SLE patients, an increase they associated with loss of barrier integrity [12]. These results suggest that SLE is associated with increased gut permeability, detectable in patients though multiple complementary markers.

An altered or imbalanced gut microbiota can promote this increased barrier permeability and, in predisposed individuals, may act as a trigger for autoimmune disease [34,37]. Recent experimental studies highlighted the role of specific microbes, such as *Enterococcus gallinarum*, which, upon translocation and colonization of secondary lymphoid tissues, can induce Th17 responses and systemic autoimmunity in mouse models [38]. In patients, Balmant et al. (2023) [37] showed that plasma levels of zonulin, an essential gut barrier protein, showed a tendency to correlate with higher CRP levels, and were inversely associated with C3 complement, even in the inactive SLE patient population analysed, further linking barrier dysfunction to immune dysregulation [39].

It is important to note that the gut microbiome is likely not the only contributor to this bacterial-induced activation. James et al. (2022) [40] found little correlation between paired gut and plasma microbial profiles of SLE patients and healthy controls. This points to the need for further exploration of other potential sources of microbial translocation, such as the oropharynx, skin, and genitourinary tract, to clarify their contributions to SLE phenotypes and outcomes, if any [40].

3.2.2. Molecular mimicry

Studies of normal human gut microbiome show abundant production of commensal-reactive antibodies and immune cells [41]. One mechanism by which this may become pathogenic is molecular mimicry, where microbial antigens resembling host proteins trigger cross-reactive immune responses in genetically predisposed hosts [2,41,42].

An example involves anti-Ro60 autoantibodies, common in SLE. Greiling et al. (2018) demonstrated the presence of Ro60 ortholog–containing commensal bacteria not only in the gut microbiome, but also in those of the mouth and skin [2]. In SLE patients positive for anti-Ro60 antibodies, T cells recognized these bacterial orthologs in vitro. In that same study, mice colonized with common human Ro60 ortholog-producing commensals mounted both T- and B-cell responses to Ro60, highlighting how mimicry might develop [2]. A targeted, antigen-driven response was also illustrated by Azzouz et al. (2019), who showed anti-dsDNA antibodies from SLE patients cross-reacted with lipoglycans from specific strains of *Ruminococcus gnavus* [11].

Similarly, *Odoribacter splanchnicus* and *Akkermansia muciniphila* produce peptides that mimic SLE autoantigens, stimulating IFNγ, IL-17 and IgG responses in patients, but not in controls [30]. Given that IL-17 can induce IgG3 class-switching and production, it is interesting to note that very recently, Gronke et al. (2025) [38] demonstrated a significant correlation of anti-*E.gallinarum* antibodies and anti-human RNA autoantibodies in SLE patients. Again, this response seems specific, and did not extend to *E. coli*, for instance. The isotype response against *E. gallinarum* in these patients was particularly strong to IgG3, particularly in those with higher disease activity.

3.2.3. Microbiome-driven immune dysregulation in SLE

As discussed above, one pathway of influence involves the production of antibodies targeting highly immunogenic bacterial components. These antibodies form immune complexes that are deposited, for instance, in the kidneys, contributing to the development of lupus nephritis (LN) [43].

Another mechanism is the microbiome's ability to enhance lymphocyte activation and promote differentiation of specific pro-inflammatory subsets. Zhang et al. (2021) analysed T, B, and NK cell counts and proportions, revealing a significant positive association between *Ruminococcus* abundance and regulatory T cell (Treg) levels [44]. In vitro studies have shown that microbiota from SLE patients stimulate lymphocyte activation and T-helper 17 (Th17) cell differentiation more effectively than microbiota from healthy controls [45] and increased Th1/Th2 and Th17/Treg ratios are seen in SLE patients, aligning with existing theories regarding SLE pathogenesis [44].

Human studies further support the role of specific microbial taxa in modulating cytokine production. For instance, *Bacteroides*, *Succinivibrio*, *Bilophila*, and *Parabacteroides* have been associated with elevated levels of pro-inflammatory cytokines such as IL-17 and IFN-γ [29]. *Lactobacillus reuteri*, in turn, has been linked to increased production of type I interferon in a TLR7-dependent way in SLE mouse models [46]. The same study also reported increased *Lactobacillus spp* in SLE patients compared to healthy controls, although no direct measurement of IFN or TLR7 signaling was performed in human samples [46]. On the other hand, *Faecalibacterium prausnitzii,* known to be reduced in SLE compared with controls [11,42] and to be negatively associated with disease activity, is thought to decrease IL-12 and IFN-γ and increase IL-10 production [43]. To complete the picture, changes in cytokine levels in steroid-treated patients were proposed by Guo and colleagues to be associated with differential changes in the microbiome of treated and untreated SLE patients [29]. These findings underscore how immune responses to commensal bacteria may contribute to lupus pathogenesis

by amplifying systemic inflammation and immune activation and how treatment might impact these pathways also due to its effects on the microbiome.

3.2.4. Metabolic changes

The influence of the gut microbiome extends beyond direct immune modulation. Changes in metabolism might be one such avenue. A large population-based study in Sweden found that gut microbiota accounted for nearly half of the variance in individual plasma metabolites, independent of lifestyle and health factors, highlighting its metabolic impact [47].

In SLE, Guo et al. (2020) identified distinct microbial genera in the gut microbiome of glucocorticoid-treated and untreated patients. Genera such as *Bacteroides*, *Parabacteroides*, *Alistipes*, *Fusobacterium*, and *Adlercreutzia*, over-represented in untreated patients, correlated with glycan, protein, and adipocytokine pathways [29], all potential contributors to SLE pathogenesis [48,49].

Bile acids, crucial for lipid digestion, also act as signaling molecules that influence various metabolic processes. Disruptions in their metabolism, potentially driven by gut microbiome alterations, could contribute to the observed lipid metabolism disturbances in SLE [50]. Additionally, He et al. (2020) showed bile acids measured in fecal samples from SLE patients were a good predictor ($R = 0{,}6$) of activity (Systemic Lupus Erythematosus Disease Activity Score, SLEDAI) scores, highlighting one possible mechanism through which dysbiosis can produce change [50].

Similarly, Chen and colleagues (2021) identified significant alterations in untreated SLE patients through gut microbiome metagenomic analysis [30]. Enriched pathways were primarily related to amino acid, lipid, and vitamin K2 metabolism, while pathways involved in peptidoglycan and branched-chain amino acid biosynthesis were reduced. These findings align with mechanistic insights from lupus mouse models, which suggest that altered microbial metabolism may contribute to disease pathogenesis. For instance, disrupted tryptophan metabolism has been implicated in gut barrier dysfunction and immune activation [51] while changes in fatty acid biosynthesis have been shown to be associated with clinical characteristics and immune responses in RA [52], though their role remains controversial [24,32].

Collectively, these findings underscore the role of gut microbial metabolism in shaping immune responses and contributing to SLE development.

3.3. Disease activity and specific organ involvement

All studies that assessed SLE activity used the SLE Disease Activity Index (SLEDAI), reflecting widespread clinical practice, though their cutoffs for defining "active" disease varied [9,24,53]. Despite the somewhat arbitrary nature of these cut-offs, a consistent finding is that microbiome changes correlated with SLE disease activity. For example, lower microbial richness was linked to higher SLEDAI scores, and differences in composition became especially pronounced in moderate-to-high activity groups [9,11,28,43]. As discussed in section 3.1, a lower *Firmicutes/Bacteroidetes* ratio characterizes SLE dysbiosis. Here we note it has also been associated with higher disease activity, with *Bacteroidetes* usually being more prevalent in more active patients [54]. Crucially, this activity-associated microbiome signature can be different from the signature that distinguishes SLE patients from healthy controls [26].

Differences are also apparent at a more granular level of analysis (Table 3). At the genus level, some taxa (e.g., *Capnocytophaga*, *Bacteroides uniformis*, *Bifidobacterium*) [11,28] were reduced in active disease, while others (*Lactobacillus salivarius*, *Streptococcus anginosus*, *Ruminococcus gnavus*) [9,11,32] increased with higher disease activity. *R. gnavus* has yielded conflicting results, being reported as both increased [11] and decreased [9] in active SLE patients compared to those in remission. Notably, Azzouz et al. pointed out only one *R. gnavus* strain significantly correlated with lupus nephritis, highlighting how specific bacterial strains may drive pathogenesis [12]. Some findings are more consistent; for example, *Bifidobacterium* appeared to be enriched only in patients with low or inactive disease [9].

Gut microbiome signatures may also potentially outperform

Table 3
Summary of taxa associated with disease activity. Results present findings supported by more than one reference only.

Taxon/Reference		[9]	[11]	[26]	[28]	[32]	[37]	[50]	[54]
Phylum	*Bacteroidota (Bacteroidetes)*								↑
	Firmicutes							↓	
	Verrucomicrobia			↑					
Class	*Bacilli*			↓					
Order	*Eubacteriales (Clostridales)*			↓					
Family	*Eubacteriaceae*			↓					
	Lactobacillaceae			↓					
	Oscillospiraceae (Ruminococcaceae)			↓					
Genus	*Acholeplasma*				↓				
	Bifidobacterium	↓							
	Campylobacter	↑							
	Capnocytophaga				↓				
	Fusicatenibacter			↓					
	Lactobacillus			↓					
	Leptotrichia				↓				
	Megamonas						↓		
	Romboutsia			↓					
	Streptococcus	↑							
	Turicibacter			↓					
Species	*Bacteroides thetaiotaomicron*			↑					
	Bacteroides uniformis		↓						
	Clostridium sp AtCC BAA-442					↑			
	Desulfovibrio piger			↑					
	Eubacterium cellulosolvens			↓					
	Faecalibacterium prausnitzii			↓					
	Fusicatenibacter saccharivorans			↓					
	Lactobacillus salivarius					↑			
	Ruminococcus gnavus	↓	↑	↑					
	Streptococcus anginosus	↑							

↑ Higher in SLE ACTIVE patients or vs SLE INACTIVE or lower in Inactive (absolute or relative abundance).
↓ Higher in SLE INACTIVE or lower in SLE ACTIVE (absolute or relative abundance).

traditional biomarkers of activity, such as anti-dsDNA antibodies and complement levels, in distinguishing active from remission states [9]. In a French cohort, unsupervised clustering of SLE patients based on gut microbiome composition identified a subgroup strongly correlated with disease activity as measured by SLEDAI. This group exhibited pronounced dysbiosis, including a reduced F/B ratio. Notably, supervised clustering of active and inactive patient groups mostly reproduced this particular microbial composition signature [26]. The relevance of these findings is increased by the fact that most patients were receiving standard treatments, such as hydroxychloroquine, reflecting real-world clinical scenarios.

Certain strains appear to "bloom" during flares, suggesting that host genetics and strain-level bacterial features could interact to affect disease course [43]. These relationships do not have to be directly between a microbe and the host, as ecological network effects also have to be taken into account. Zegarra-Ruiz et al. (2019) reported *Lactobacillus* spp. enrichment in fecal samples from a subset of patients who presented simultaneously reduced levels of bacteria from the order *Clostridiales* [46].

Together, these findings support the idea that the gut microbiome may both reflect and influence SLE disease activity.

In addition to broad systemic effects, some studies suggest that microbiome alterations in SLE may be associated with specific organ manifestations. Although findings remain preliminary, highlighting these reported associations (Table 4) may be helpful to clinicians seeking to contextualize emerging microbiome data in relation to disease heterogeneity.

3.3.1. Lupus nephritis

Lupus nephritis (LN) affects up to 60 % of SLE patients and is a major contributor to long-term morbidity and mortality [55]. In a recent large survey of European patients, at least 30 % reported some kidney involvement, reinforcing both its prevalence and impact from the patient perspective [56]. Of all the organ systems affected in SLE, LN has received particular attention and has provided the most evidence for the role of the gut microbiome in this disease.

Ruminococcus gnavus has been positively associated with SLE in multiple studies involving human patients, particularly with nephritis [11,26,32,54]. However, the increase in *R. gnavus* was not universally observed or significant across all studies on LN [18,54]. Some associations may depend on specific species or even strain-level characteristics, as discussed above regarding Azzouz et al.(2019) [11]. Some of this variability may also reflect the taxonomic ambiguity present in the literature due to reclassification over time. *R. gnavus* is a pertinent example of this, having been reassigned to the *Lachnospiraceae* family and now referred to as *Blautia* (*Ruminococcus) gnavus* [57] (referred to as *R. gnavus* throughout this review for consistency).

3.3.2. Neuropsychiatric lupus

Neuropsychiatric symptoms are common in SLE, encompassing a broad spectrum of manifestations including depression and anxiety, cognitive dysfunction, seizures and psychosis [58]. The biggest survey of SLE patients in Europe showed almost half of them reported depression or anxiety as current symptoms, and around 15 % selected these manifestations as what worried them the most and identified them as the main barrier to living life to the fullest [59].

Yao et al. (2022) investigated the gut microbiome composition in 38 SLE patients, comparing those with depression to those without, as assessed by the Self-Rating Depression Scale [19]. All patients were classified as inactive or mildly active based on the SLEDAI-2 K score and were on low doses of corticosteroids (less than 10 mg) and/or hydroxychloroquine.

The study found a distinct gut microbiome composition between SLE patients with and without depression, with reduced alpha-diversity in the depression group, as well as altered abundance of specific genera, including *Faecalibacterium*, *Roseburia*, and *Bacteroides*. These differences were accompanied by altered fecal metabolites and correlated with higher IL-2 and IL-6 levels, along with lower brain-derived neurotrophic factor in the depressed group compared to the non-depressed group [19].

3.3.3. Immunologic manifestations

Immunologic abnormalities — including autoantibodies such as ANA and anti-dsDNA and low complement levels — are integral to SLE classification, associated with disease activity and organ involvement and used routinely in clinical monitoring [60].

Microbial alterations may reflect or contribute to the underlying immunologic manifestations in SLE. For instance, López et al. (2016) reported a reduced frequency of *Synergistetes* in SLE patients with high levels of anti-dsDNA autoantibodies [45].

Similarly, Azzouz et al. (2019) found that antibodies against specific strains of *Ruminococcus gnavus* were directly correlated with anti-dsDNA autoantibody levels and inversely correlated with complement levels in patients exhibiting increased expression of this species in their gut [11].

Table 4
Summary of taxa associated with specific organ involvement in SLE. Results present findings supported by more than one reference only.

Taxon/Reference		[11]	[19]	[20]	[28]	[32]	[54]
Phylum	*Epsilonbacteraeota*		↓Depression				
	Patescibacteria		↓Depression				
	Synergistetes		↓Depression				
	Verrucomicrobiota		↓Depression				
Family	*Lactobacillaceae*		↑Depression				
Genus	*Bifidobacterium*				↓Articular		
	Blautia		↑Depression				
	Campylobacter						↑Kidney
	Lactobacillus		↑Depression				
	Streptococcus			↑ Kidney			
	Turicibacter			↓Kidney			
Species	*Actinomyces johnsonii*					↑Kidney	
	Clostridium nexile					↑Kidney	
	Enterococcus avium					↑Kidney	
	Olsenella uli					↑Kidney	
	Ruminococcus gnavus	↑Kidney				↑Kidney	
	Staphylococcus aureus					↑Kidney	
	Veillonella dispar	↑Kidney					
	Veillonella parvula	↑Kidney					

↓Lower in patients with organ affected (absolute or relative abundance).
↑ Higher in patients with organ affected (absolute or relative abundance).

3.4. Treatment and microbiome

The relationship between the gut microbiome and treatments has been explored in a bidirectional way. Standard of care treatments in SLE, primarily oral chemical compounds that are absorbed in the gastrointestinal tract, can influence the microbiome. Conversely, the dysbiosis observed in SLE patients and other inflammatory diseases offers potential for disease modulation through targeted interventions in the gut microbiome. An overview of key findings from human studies is provided in Table 5.

3.4.1. Microbiome modulation from treatment

Many of the studies done on SLE patients reported here either excluded some drugs or established some limits to their dose (e.g. PDN > 10 mg/day). Interestingly, a recent longitudinal study found hydroxychloroquine and low dose prednisolone to have no correlation with differences in microbiome diversity or variation [43].

3.4.1.1. Corticosteroids. By dampening the immune response, steroids might affect the host's ability to control microbial populations. Additional influences, such as changing pH levels in the gastrointestinal tract, can also affect bacteria [61].

Guo et al. (2020) specifically compared steroid-treated and untreated SLE patients, finding that glucocorticoid-treated patients exhibited microbial bacterial diversity and a F/B ratio similar to that healthy controls, regardless of their disease activity (SLEDAI-2 K <6 or ≥ 6) [29]. However, patients on glucocorticoids still displayed differences compared to healthy controls, suggesting that further research is needed to determine whether these differences are consistent, influenced by steroid dosage, or affected by individual susceptibility and environmental factors. Notably, the study did not include pre-treatment assessments, limiting the ability to make paired comparisons.

The authors also highlighted that corticosteroid treatment in SLE patients is linked to an enrichment of short-chain fatty acid (SCFA)-producing bacteria, raising the possibility that glucocorticoids may exert additional mechanisms of action in SLE beyond their immunosuppressive effects [29].

3.4.1.2. Antimalarials. Hydroxychloroquine (HCQ) is a cornerstone treatment for SLE. It is also used in other immune-mediated diseases, in which its influence on the gut microbiome has been recognized. In RA, for instance, HCQ use is associated with increased microbial diversity and a rise in anti-inflammatory species [62].

In SLE mouse models, HCQ has been shown to induce specific changes in bacterial taxa, such as a reduction in the abundance of *Oscillospira* and an increase in *Bifidobacterium* [63]. Notably, in that same study, *Dialister* was decreased by HCQ in mice [63]. This contrasts with findings in SLE patients where decreases in the genus distinguished SLE from healthy controls [13] and increased *Dialister* was associated with remission as well as negatively associated with IL-17, IL-2R and IL-35 [29].

In human studies, Guo et al. (2020) assessed patients based on treatment status, comparing glucocorticoid-free patients (only on HCQ) with glucocorticoid-treated patients and healthy controls. The HCQ-only group exhibited higher gut microbial diversity than healthy controls, although they showed reduced evenness (as measured by Pielou's index) without differences in the Shannon index [29].

There is very limited data, so far, regarding the specific effects of other disease modifying drugs (DMARDs) on the gut microbiome of patients with SLE, but some other commonly prescribed drugs have been studied.

3.4.1.3. Proton pump inhibitors. Proton pump inhibitors (PPIs) are commonly co-prescribed with corticosteroids to mitigate the risk of gastrointestinal ulceration and bleeding, as well as to alleviate heartburn symptoms associated with gastroesophageal reflux disease, which is a prevalent finding in the general population and particularly in steroid-treated patients.

PPIs are believed to significantly impact the gut microbiome by reducing gastric acidity, potentially compromising the immunological barrier to infection and allowing for increased colonization by environmental microorganisms, starting with the oral microbiome [64].

Li et al. (2022) specifically examined the influence of PPIs on the gut microbiome composition in SLE patients [15]. Their findings indicated that PPI use brought the microbiome composition of SLE patients closer to that of healthy controls compared to SLE patients not using PPIs. Although the study included two comparison groups—SLE patients without PPIs and healthy controls—the SLE group without PPIs had notable differences compared to the group using PPIs, such as longer disease duration, higher HCQ use, and less immunosuppressant treatment. Nonetheless, redundancy analysis revealed that PPI use was the only significant explanatory variable in this small sample.

The authors proposed a tentative pathogenic explanation, suggesting that PPIs may influence metabolic pathways by affecting the abundance

Table 5
Summary of taxa associated with treatments.

Taxon/Reference		[15]	[29]	[46]	[54]	[63]	[69]	[70]
Phylum	*Bacteroidota (Bacteroidetes)*				↑Probiotics			↑FMT
	Firmicutes							↓FMT
Order	*Enterobacterales*		↓Corticosteroids					
Genus	*Alipipes*	↑PPIs						
	Bifidobacterium		↓Corticosteroids			↓HCQ	↓Diet[¥]	
	Dialister					↑HCQ		
	Escherichia	↑PPIs						
	Lactobacillus						↓Diet[*]	
	Morganella	↑PPIs						
	Oscillospira					↑HCQ		
	Roseburia	↑PPIs						
	Stenotrophomonas	↑PPIs						
	Streptococcus		↓Corticosteroids					
Species	*Bifidobacterium bifidum, B. breve, and B. longum*							↓FMT
	Lactobacillus reuteri			↑Diet[¤]				
	Ruminococcus gnavus				↑Probiotics			

↑ Treatment results in increased absolute or relative abundance.
↓ Treatment results in decreased absolute or relative.
FMT – Fecal Microbiota Transplantation; HCQ – Hydroxychloroquine; PPIs - Proton Pump Inhibitors.
[*] Flavanones (from oranges).
[¥] Dihydrochalcones (from apples).
[¤] Fiber

of specific genera, including *Escherichia*, *Roseburia, Stenotrophomonas, Morganella,* and *Alipipes* in SLE patients [15].

3.4.2. Microbiome modulation as treatment

The impact of dietary changes on the microbiome and disease activity in SLE has been studied for some time. However, interventional studies in patients have only recently emerged. Additionally, microbiome modulation may offer benefits beyond direct treatment goals. In mouse models, changes to the microbiota have been shown to enhance the effectiveness of corticosteroid treatment [65].

3.4.2.1. Diet. Intuitively, it is expected that diet can affect the microbiome. Recent studies have demonstrated just how responsive to changes in alimentary habits the microbiome is [66]. Along with modulating the microbiome, diet can also influence host immune responses [4].

The direct effect of diet has also been studied on SLE, both from the point of view of pathogenesis and immunomodulation [67,68]. In women with inactive SLE, higher sodium intake was associated with lower complement levels, indicating a potential link between dietary salt and immune regulation [37]. Experimental studies further support this, with high-salt diets shown to alter immune responses in lupus-prone mice and promote T follicular helper (Tfh) cell differentiation in vitro [61]. As Tfh cells enhance B cell activation, their expansion may amplify autoantibody production, contributing to lupus pathogenesis.

Interestingly, intake of fiber-rich foods, particularly those containing resistant starch, which is fermented to SCFA by the gut microbiome, helped restore the abundance of bacteria reduced in the lupus-prone mouse model [46]. This modulation resulted in lower levels of the pathogenic *Lactobacillus reuteri*, which, in turn, was associated with improved clinical outcomes [46].

In turn, Cuervo et al. (2015), analysed the relationship between polyphenols and the gut microbiome in 20 SLE patients and 20 age-matched controls [69]. They found flavanones from oranges were positively associated with the proportions of *Lactobacillus*, while dihydrochalcones from apples were linked to *Bifidobacterium* levels in SLE patients. As discussed above, despite some specific cases, both these bacteria are frequently reported as beneficial in SLE [69].

3.4.2.2. Probiotics. Widhani et al. (2022) conducted a randomized, double-blind, placebo-controlled trial to assess the effects of a 60-day supplementation with capsules containing a combination of probiotics (live beneficial bacteria) and prebiotics (non-digestible substances that promote gut bacteria growth) in active SLE patients. Specifically, the active supplementation group received capsules containing *Lactobacillus helveticus*, *Bifidobacterium infantis*, *Bifidobacterium bifidum,* and fructo-oligosacharides, whereas the placebo group received similar-looking capsules with *Saccharum lactis* [54].

The supplementation led to a statistically significant reduction in *Bacteroidetes* after 60 days and an increase in the F/B ratio, although the latter change was not statistically significant. As stated above, both of these changes were generally associated with lower activity in SLE patients. Notably, the SLEDAI score decreased by 6 points in the supplementation group, while it remained stable in the placebo group. However, the pre-treatment SLEDAI scores differed significantly between the two groups, with the supplementation group starting at an SLEDAI-2 K of 14 compared to 9 in the placebo group. This baseline imbalance may have influenced the observed effects, as a higher initial SLEDAI score could have allowed for a greater potential reduction, independent of the intervention.

The mechanisms behind the observed effects may involve various processes. In the same study [54], probiotic supplementation reduced *Ruminococcus gnavus* abundance, a taxon previously linked to SLE and disease activity, which could explain the impact of supplementation.

It is important to note that all patients received standard of care treatment, which may confound the results, and they were recruited based on unspecified gastrointestinal symptoms, raising the question of latent gastrointestinal problems that might bias the results.

Nonetheless, in vitro studies showed that adding *Bifidobacterium bifidum*, a commonly used probiotic, to fecal microbiota samples from SLE patients have prevented the overactivation of CD4+ T cells observed in control samples [45].

3.4.2.3. Fecal microbiota transplantation. Given the dysbiosis observed in SLE patients, it is logical to explore whether fecal microbiota transplantation (FMT) could improve gut microbiome composition and function, potentially alleviating SLE symptoms. In the first multicentric, single-arm, open-label trial, Huang et al. (2022) administered weekly oral capsules of fecal microbiota from healthy donors (without antibiotic "pre-clearing") to 20 patients with active SLE (SLEDAI >6), alongside standard care [70]. Eighteen completed the 12-week follow-up (one received antibiotics and was excluded; one withdrew due to an unspecified adverse event). SLEDAI scores dropped from 9.45 to 6.61, and 42 % met an SRI-4 response threshold. FMT restored some aspects of microbial richness and diversity, shifting the gut microbiota closer to that of healthy controls [70].

Notably, a 14-species microbial "signature" predicted treatment response with high accuracy (AUC of 0.89). Responders showed enrichment of short-chain fatty acid (SCFA)-producing taxa, higher SCFA levels, alongside reduced IL-6, and fewer circulating CD4+ memory T cells. *Bifidobacterium* correlated with expansion of CD4+ naïve T cells, while butyric and isovaleric acids paralleled rises in IL-10 [70]. The authors suggest these changes may promote a more tolerogenic immune state via downregulation of co-stimulatory molecules on antigen-presenting cells (APCs) [70].

Follow-up work in the same cohort revealed higher DNA methylation in immune-regulatory regions among responders, implicating SCFAs—particularly butyrate—in driving altered gene expression [71,72]. Single-cell analyses further indicated that responders had reduced interferon-driven pathways in T, B, and NK cells, whereas non-responders maintained elevated immune activation [60].

> *Overall, these findings highlight FMT's potential not only to rebalance the microbiota but also to modulate immune mechanisms through metabolic and epigenetic pathways. While larger trials are needed to confirm efficacy and safety, such data underscore the transformative possibilities of microbiome-based interventions in SLE.*

4. Discussion

This narrative review organizes evidence along a clinical pathway — from diagnosis to monitoring and treatment — to highlight the importance and relevance of gut microbiome findings for clinicians and better support translational insights. Through this lens, we show how dysbiosis in SLE encompasses reduced microbial richness, shifts in community structure, and enrichment of specific taxa that may correlate with disease activity. This growing body of evidence supports an active role of the gut microbiome in SLE, with potential implications for clinical practice. However, the significant heterogeneity in microbial profiles across cohorts, further complicated by the disease's variable clinical presentation and treatment regimens, underscores the need for cautious interpretation and further validation. While there are potential opportunities for innovative, personalized biomarker and therapeutic strategies, such approaches remain exploratory and are likely to be medium- to long-term developments.

Investigating the gut microbiome's role in SLE is most informative when focusing on human studies. While mouse models offer mechanistic insights and indirect parallels (e.g., histopathology), they do not capture the entire complexity of human SLE—particularly regarding clinical manifestations like neuropsychiatric symptoms. Additionally, different

hosts might result in substantially different impacts on the microbiome. For instance, lupus-prone murine models often exhibit greater microbiome diversity during disease progression, diverging from the reductions typically reported in active SLE patients [73]. These discrepancies highlight the need for cautious interpretation of mouse studies, at the same time reinforcing the importance of human-focused research, which is a particular strength of this review.

Across human studies, one commonly observed alteration in SLE is a decreased F/B ratio, a pattern shared with other autoimmune diseases such as diabetes and Crohn's disease [74], and even suggested as a diagnostic and activity biomarker [54]. This reduced ratio, however, was not universally reported, with some studies not finding significant changes, perhaps attributable to differences in the population, or the disease manifestations. Interestingly, variations in the F/B ratio can vary across autoimmune diseases — falling in SLE, multiple sclerosis and Sjögren's syndrome and rising in RA, for instance [75–77]. Such differences emphasize how immune–microbiome crosstalk may be disease-specific, shaped by local immune contexts and host genetics and requiring tailoring of microbiome research to individual diseases.

The full complexity of the microbiome and its interactions will likely only be revealed by multiple research avenues. For instance, microbial metabolism studies contrast with the F/B ratio discussed above, showing dietary patterns rich in processed foods correlate with increased *Firmicutes* abundance and inflammatory endotoxin synthesis pathways in inflammatory bowel disease patients [78,79].

Dysbiosis could potentially be detrimental, through immune activation, barrier disruption, or pathogenic expansions. Alternatively, it may be at least partially adaptive, for instance, through competitive loss of species that might otherwise aggravate inflammation in different contexts. Germ-free mice show attenuated autoimmunity. In contrast microbiome transplants from SLE patients induce lupus-like phenotypes in healthy mice, including autoantibodies, cellular proliferation and cytokine production, suggesting a pathogenic capacity in certain SLE-associated consortia [22,80].

Two different studies have tried to disentangle the cause-or-consequence dilemma of dysbiosis in SLE - both as a potential driver of disease and a reflection of its systemic effects. Using Mendelian randomization (MR) methods to minimize the confounding and reverse causation in traditional observational studies, both found supporting causal links between specific bacterial classes (e.g., *Bacilli*, *Lactobacillales*) or genera (e.g., *Bifidobacterium, Eggerthella, Ruminococcus*) and SLE, as well as some that worked to reduce the risk of SLE (e.g., *Bacillales*, *Coprobacter* and *Lachnospira*) [81,82], though some species also play contrasting roles across distinct autoimmune conditions [82].

The need to study the disease-specific interaction with the host is exemplified by *Enterococcus gallinarum*, a Gram-positive gut commensal, detected in liver biopsies of SLE patients with autoimmune hepatitis, but not in those of healthy controls. Using mouse models, Manfredo Vieira et al. (2018) went further in establishing that *E. gallinarum* acts to alter gut permeability, down-regulating molecules involved in barrier adhesion, mucus formation and antimicrobial defense [83]. Very recent work from the same group has shown *E. gallinarum* to promote expansion of Th17 cells and an increase in IgG3 autoantibodies against RNA-protein complexes, linking barrier dysfunction, T-cell polarization and autoantibody production centered around this pathobiont [38].

Unsurprisingly, it is not only the gut microbiome that seems capable of eliciting immune responses, increasing the scope for interactions. When comparing the vaginal and gut microbiota of SLE patients and healthy controls, the vaginal microbiome in SLE patients displayed higher richness and diversity than their gut microbiome, which, in turn, was less rich than that of healthy controls [17]. Vaginal microbial changes correlated significantly with immunological markers, suggesting that the vaginal microbiome may be affected earlier than the gut, or simply be more sensitive to SLE's pathogenesis or treatment effects. This finding is significant because it highlights the potential for different microbiome sites to play distinct roles in immune interactions, opening new avenues for clinically actionable strategies.

Additionally, distinct compartments *within* each local microbiome might influence and interact with one another, further shaping immune responses. For example, Tomofuji et al. (2021) found that SLE patients had fewer viral phages, including crAss-like phages, a recently identified group of bacteriophages that are abundant in the healthy gut virome, primarily infecting *Bacteroidetes*, but also some *Firmicutes* such as *Ruminococcus*. This reduction could thus allow the proliferation of *Ruminococcus*. The researchers also noted a symbiotic link between *Podoviridae* phages and *Faecalibacterium*; in SLE, *Podoviridae* levels were substantially lower, mirroring a drop in *Faecalibacterium* and indicating a disrupted phage–bacterium network in the disease [84].

Perhaps not surprising in a disease with a female-to-male imbalance such as SLE, host characteristics, such as gender and age, also appear to play an active role in shaping the gut microbiome. Albeit in mouse models, Silverman et al. (2022) showed colonization of females with *Ruminococcus* resulted in significantly higher gut permeability compared to males [85]. Parallels between microbiome alterations in SLE patients and those seen in aging populations are also particularly noteworthy. Both groups of individuals experience reduced microbial diversity, increased gut permeability, and inflammatory shifts involving taxa like *Enterococcus* and *Ruminococcus gnavus* [86].

Recent findings, beyond the December 2023 cut-off date used for this review, further support and expand on the conclusions drawn. In particular, Zhou et al. (2025) [87] conducted a large-scale, multidisease cohort, metagenomic analysis of the gut microbiome of several immune-mediated diseases and colorectal cancer. They identified SLE and inflammatory bowel disease as sharing microbial and functional signatures. Importantly, the authors focused on how these microbial changes might interact with the immune system of the host to produce disease, for example, by binding proteins involved in inflammation such as specific glucocorticoid receptors.

We found only a minority of studies assessed the association between specific taxa and peripheral immune features such as cytokines, immune cell subsets, or autoantibody levels. Where explored, these relationships suggest that certain microbes may not merely mark disease presence, but may actively modulate immune function. Integrating microbiome and immune profiling in future studies could uncover mechanistically relevant taxa and guide targeted validation studies.

Overall, these findings emphasize the reciprocal interplay between host and microbiome, where host-specific traits drive microbial composition and functionality, potentially amplifying or mitigating disease processes like SLE. Indeed, Bagavant et al. (2021) identified anti-*Enterococcus gallinarum* antibodies in both SLE patients and healthy controls. However, not only were these higher in SLE, but those patients with anti-dsDNA, anti-Sm and anti-RibosomalP autoantibodies had higher titers [88]. This may suggest pathobiont potential requires susceptibility by the host's immune system.

Several studies correlating microbiome signatures with disease activity were conducted in patients already receiving treatment. This suggests that microbiota-based models may retain discriminatory value even in treated populations. While promising, their use in disease monitoring remains exploratory. The various treatments that SLE patients receive in the management of the disease might not only influence study variables but also provide additional insights into the interplay between the gut microbiome and treatment outcomes. As shown above, corticosteroids, for example, partially restore the F/B ratio, while HCQ influences microbial diversity and promotes species with anti-inflammatory properties. It is also clear that these treatments received more attention than newer therapeutic options currently in use for SLE such as biologics (e.g. rituximab, belimumab, and anifrolumab). As bigger SLE patient populations are included in microbiome studies, it will be interesting to focus on treatment-specific microbiome signatures or whether these associate with response or toxicity.

Moving forward, targeted modulation of the gut microbiome could constitute a potential therapeutic avenue [89]. Dietary interventions,

such as polyphenol-rich or high-fiber diets, show promise in modulating microbiome composition, including reducing pro-inflammatory taxa like *Lactobacillus reuteri* [46,69]. Conceivably, they could be part of a strategy to maintain compositionally and functionally balanced microbiotas, contributing to disease prevention or remission maintenance. A fascinating option raised by Manfredo Vieira et al. (2018) is using the immune response to control the microbiome, thus stopping the pathogenesis of an autoimmune disease. The group showed an intramuscular vaccine against *E. gallinarum* had the potential to prevent disease pathogenesis in mouse models [33].

During periods of disease activity, antibiotic treatment, possibly combined with pro and prebiotics, could be used [89]. In mouse models, this approach prevented mortality and mitigated pathologic changes associated with SLE, through suppression of *E. gallinarum* [83]. While these approaches hold promise, further research is needed to determine their translational potential and applicability in human patients.

Already used for treating refractory *Clostridioides* infection, FMT is emerging as a promising approach for modulating the gut microbiome in various conditions, including SLE [89]. As highlighted earlier, preliminary evidence has demonstrated benefits of FMT in a small sample of human SLE patients, including improvements in microbiome diversity and clinical outcomes. Although larger trials are needed to confirm efficacy and safety, and to dissect mechanisms, these interventions highlight the translational potential of microbiome therapeutics.

Despite these promising developments, the heterogeneity in study design, sample size, methodology (e.g., sequencing platforms, taxonomic resolution), and clinical outcome definitions among the included studies poses a challenge for direct comparison and generalization of findings. Although we did not conduct a formal risk-of-bias assessment, the possibility of publication bias—particularly favouring studies reporting positive associations—should be acknowledged. We note a geographic concentration of studies hailing from China, potentially introducing regional bias in the findings, as specific local environmental exposures may influence the results, for instance. Most research relies on relative, rather than absolute, microbial assessments, potentially overlooking critical species. Taxonomic revisions can affect classification and may account for discrepancies in microbiome studies, depending on the bioinformatic pipeline used. For example, *Ruminococcus gnavus* has been reclassified under *Blautia*, which may influence how it is interpreted across datasets [57]. These limitations highlight the complementary importance of strain-level and function-based analyses [57]. Moreover, limited focus on other components of the microbiome restricts our understanding of the broader microbial ecosystem in SLE, with only a handful of studies examining the fungal gut microbiome [90,91] or the gut virome [16,84,92]. More robust, longitudinal and multinational human studies are needed to identify consistent microbial signatures and track changes over the disease course. Additional efforts should examine how the wider environment, including social determinants of health (e.g., ethnicity and socioeconomic status) shape the microbiome and disease expression.

Looking ahead, the microbiome's value as a biomarker hinges on pinpointing which shifts most accurately reflect disease activity or predict flares, across diverse populations and disease states. Advancing cost-effective, standardized sequencing and analysis methods will facilitate generalization. This would be helped by a minimum reporting standard in future gut microbiome studies, for instance for diversity metrics, to facilitate a common language. Additionally, most of the research is still focused on taxonomic composition. There is a need for studies to move beyond and assess microbial functionality to support discovery of disease mechanisms and biomarkers. Multidimensional datasets, combining not only microbiome composition and functionality, but also immune phenotyping, metabolomic profiling, and clinical endpoints such as manifestations, activity, and treatment response should help assess and optimize the best path forward in potential clinical implementations. These insights will be particularly valuable when paired with tailored interventions.

In summary, the gut microbiome emerges as a dynamic, multifaceted player in SLE pathogenesis. A key strength of this review, integrating human-focused findings with the mechanistic depth offered by animal models, reveals both promising therapeutic prospects and pressing knowledge gaps, particularly as analytical tools continue to evolve and are brought ever closer to clinical practice. These insights, coupled with the growing evidence for dietary and microbial interventions—including targeted antibiotic use and FMT—offer exciting prospects for personalized approaches to SLE management.

5. Conclusion

The current literature provides compelling evidence for a role of the gut microbiome in SLE, influencing disease pathogenesis, activity, and treatment outcomes. Over the past decade, the field has progressed from animal studies to human-centered research, exposing intersections between dysbiosis and clinical manifestations and redefining the microbiome into a potentially actionable target rather than an incidental factor.

This narrative review organizes findings along the clinical pathway, from diagnosis to therapy, to help clinicians contextualize microbiome research in relation to real-world care. Our findings emphasize how microbiota-informed signatures may eventually complement conventional biomarkers for disease stratification, activity assessment, or therapeutic responsiveness. However, methodological variability, limited cohort diversity, and insufficient mechanistic clarity constrain translation into practice. Achieving clinical integration will require harmonizing research approaches, accounting for environmental factors, and conducting longitudinal studies with diverse populations.

Emerging interventions, such as dietary modulation, probiotics, and fecal microbiota transplantation, offer promising pathways to therapeutic options. Bridging these insights into practice will require both scientific advancements and clinical collaboration. As these initiatives mature, the gut microbiome may emerge as a much needed and valuable tool for more individualized, biologically-informed, and effective care in SLE.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT-v4o (OpenAI) to improve the quality of written English and enhance the flow of the manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Funding

This work was supported by a PhD grant by FCT – Fundação para a Ciência e Tecnologia to DGO (UI/BD/150742/2020) and UMIB (UIDB/00215/2020; UIDP/00215/2020; LA/P/0064/2020) and Bolsa de Doutoramento (PhD grant) Nuno Grande (2022) by Instituto de Ciências Abel Salazar, Universidade do Porto e Fundação Bial to DGO.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgements

The authors thank Prof. Paulo Pinho e Costa for his insights into the microbiome and support for the group's projects.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2025.103921.

Data availability

Data will be made available on request.

References

[1] Arnaud L, Chasset F, Martin T. Immunopathogenesis of systemic lupus erythematosus: an update. Autoimmun Rev 2024;23:103648. https://doi.org/10.1016/j.autrev.2024.103648.

[2] Greiling TM, Dehner C, Chen X, Hughes K, Iñiguez AJ, Boccitto M, et al. Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. Sci Transl Med 2018;10:eaan2306. https://doi.org/10.1126/scitranslmed.aan2306.

[3] Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014;157:121–41. https://doi.org/10.1016/j.cell.2014.03.011.

[4] Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. Nature 2011;474:327–36. https://doi.org/10.1038/nature10213.

[5] Katz-Agranov N, Zandman-Goddard G. The microbiome and systemic lupus erythematosus. Immunol Res 2017;65:432–7. https://doi.org/10.1007/s12026-017-8906-2.

[6] Mousa WK, Chehadeh F, Husband S. Microbial dysbiosis in the gut drives systemic autoimmune diseases. Front Immunol 2022;13:906258. https://doi.org/10.3389/fimmu.2022.906258.

[7] Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. Nutrients 2012;4:1095–119. https://doi.org/10.3390/nu4081095.

[8] Gotschlich EC, Colbert RA, Gill T. Methods in microbiome research: past, present, and future. Best Pract Res Clin Rheumatol 2019;33:101498. https://doi.org/10.1016/j.berh.2020.101498.

[9] Li Y, Wang H-F, Li X, Li H-X, Zhang Q, Zhou H-W, et al. Disordered intestinal microbes are associated with the activity of Systemic Lupus Erythematosus. Clin Sci 2019;133:821–38. https://doi.org/10.1042/CS20180841.

[10] van der Meulen TA, Harmsen HJM, Vila AV, Kurilshikov A, Liefers SC, Zhernakova A, et al. Shared gut, but distinct oral microbiota composition in primary Sjögren's syndrome and systemic lupus erythematosus. J Autoimmun 2019;97:77–87. https://doi.org/10.1016/j.jaut.2018.10.009.

[11] Azzouz D, Omarbekova A, Heguy A, Schwudke D, Gisch N, Rovin BH, et al. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. Ann Rheum Dis 2019. https://doi.org/10.1136/annrheumdis-2018-214856.

[12] Battaglia M, Garrett-Sinha LA. Bacterial infections in lupus: roles in promoting immune activation and in pathogenesis of the disease. J Transl Autoimmun 2021;4:100078. https://doi.org/10.1016/j.jtauto.2020.100078.

[13] He Z, Shao T, Li H, Xie Z, Wen C. Alterations of the gut microbiome in Chinese patients with systemic lupus erythematosus. Gut Pathog 2016:8. https://doi.org/10.1186/s13099-016-0146-9.

[14] Wei F, Xu H, Yan C, Rong C, Liu B, Zhou H. Changes of intestinal flora in patients with systemic lupus erythematosus in northeast China. PLoS One 2019;14:e0213063. https://doi.org/10.1371/journal.pone.0213063.

[15] Li X-B, Chu X-J, Cao N-W, Wang H, Fang X-Y, Fan Y-G, et al. Proton pump inhibitors induce changes in the gut microbiome composition of systemic lupus erythematosus patients. BMC Microbiol 2022;22:117. https://doi.org/10.1186/s12866-022-02533-x.

[16] Chen B, Cao J, Liu W, Zhang Y, Liu Y, Wang M, et al. Disturbed gut virome with potent interferonogenic property in systemic lupus erythematosus. Sci Bull 2023;68:295–304. https://doi.org/10.1016/j.scib.2023.01.021.

[17] Ling Z, Cheng Y, Gao J, Lei W, Yan X, Hu X, et al. Alterations of the fecal and vaginal microbiomes in patients with systemic lupus erythematosus and their associations with immunological profiles. Front Immunol 2023;14:1135861. https://doi.org/10.3389/fimmu.2023.1135861.

[18] Tomofuji Y, Maeda Y, Oguro-Igashira E, Kishikawa T, Yamamoto K, Sonehara K, et al. Metagenome-wide association study revealed disease-specific landscape of the gut microbiome of systemic lupus erythematosus in Japanese. Ann Rheum Dis 2021;80:1575–83. https://doi.org/10.1136/annrheumdis-2021-220687.

[19] Yao H, Yang H, Wang Y, Xing Q, Yan L, Chai Y. Gut microbiome and fecal metabolic alteration in systemic lupus erythematosus patients with depression. Front Cell Infect Microbiol 2022;12:1040211. https://doi.org/10.3389/fcimb.2022.1040211.

[20] Wang X, Shu Q, Song L, Liu Q, Qu X, Li M. Gut microbiota in systemic lupus erythematosus and correlation with diet and clinical manifestations. Front Med 2022;9:915179. https://doi.org/10.3389/fmed.2022.915179.

[21] Di Pierro F. Gut microbiota parameters potentially useful in clinical perspective. Microorganisms 2021;9:2402. https://doi.org/10.3390/microorganisms9112402.

[22] Yamamoto EA, Jørgensen TN. Relationships between vitamin D, gut microbiome, and systemic autoimmunity. Front Immunol 2020;10:3141. https://doi.org/10.3389/fimmu.2019.03141.

[23] Hevia A, Milani C, Lopez P, Cuervo A, Arboleya S, Duranti S, et al. Intestinal dysbiosis associated with Systemic Lupus Erythematosus. mBio 2014:5. https://doi.org/10.1128/mBio.01548-14.

[24] Rodríguez-Carrio J, López P, Sánchez B, González S, Gueimonde M, Margolles A, et al. Intestinal dysbiosis is associated with altered short-chain fatty acids and serum-free fatty acids in Systemic Lupus Erythematosus. Front Immunol 2017;8:23. https://doi.org/10.3389/fimmu.2017.00023.

[25] Gerges MA, Esmaeel NE, Makram WK, Sharaf DM, Gebriel MG. Altered profile of fecal microbiota in newly diagnosed Systemic Lupus Erythematosus egyptian patients. Int J Microbiol 2021;2021:1–7. https://doi.org/10.1155/2021/9934533.

[26] Toumi E, Goutorbe B, Plauzolles A, Bonnet M, Mezouar S, Militello M, et al. Gut microbiota in systemic lupus erythematosus patients and lupus mouse model: a cross species comparative analysis for biomarker discovery. Front Immunol 2022;13:943241. https://doi.org/10.3389/fimmu.2022.943241.

[27] Ma Y, Guo R, Sun Y, Li X, He L, Li Z, et al. Lupus gut microbiota transplants cause autoimmunity and inflammation. Clin Immunol Orlando Fla 2021;233:108892. https://doi.org/10.1016/j.clim.2021.108892.

[28] Liu F, Ren T, Li X, Zhai Q, Xu X, Zhang N, et al. Distinct microbiomes of gut and saliva in patients with Systemic Lupus Erythematosus and clinical associations. Front Immunol 2021;12:626217. https://doi.org/10.3389/fimmu.2021.626217.

[29] Guo M, Wang H, Xu S, Zhuang Y, An J, Su C, et al. Alteration in gut microbiota is associated with dysregulation of cytokines and glucocorticoid therapy in systemic lupus erythematosus. Gut Microbes 2020;11:1758–73. https://doi.org/10.1080/19490976.2020.1768644.

[30] Fonseca S, Carvalho AL, Miquel-Clopés A, Jones EJ, Juodeikis R, Stentz R, et al. Extracellular vesicles produced by the human gut commensal bacterium Bacteroides thetaiotaomicron elicit anti-inflammatory responses from innate immune cells. Front Microbiol 2022;13:1050271. https://doi.org/10.3389/fmicb.2022.1050271.

[31] Chow J, Tang H, Mazmanian SK. Pathobionts of the gastrointestinal microbiota and inflammatory disease. Curr Opin Immunol 2011;23:473–80. https://doi.org/10.1016/j.coi.2011.07.010.

[32] Chen B, Jia X, Xu J, Zhao L, Ji J, Wu B, et al. An autoimmunogenic and proinflammatory profile defined by the gut microbiota of patients with untreated Systemic Lupus Erythematosus. Arthritis Rheumatol 2021;73:232–43. https://doi.org/10.1002/art.41511.

[33] Rojo D, Hevia A, Bargiela R, López P, Cuervo A, González S, et al. Ranking the impact of human health disorders on gut metabolism: systemic lupus erythematosus and obesity as study cases. Sci Rep 2015;5:8310. https://doi.org/10.1038/srep08310.

[34] Chelakkot C, Ghim J, Ryu SH. Mechanisms regulating intestinal barrier integrity and its pathological implications. Exp Mol Med 2018;50:1–9. https://doi.org/10.1038/s12276-018-0126-x.

[35] Pereira MS, Kriegel MA. Evolving concepts of host–pathobiont interactions in autoimmunity. Curr Opin Immunol 2023;80:102265. https://doi.org/10.1016/j.coi.2022.102265.

[36] Gudi R, Kamen D, Vasu C. Fecal immunoglobulin A (IgA) and its subclasses in systemic lupus erythematosus patients are nuclear antigen reactive and this feature correlates with gut permeability marker levels. Clin Immunol 2022;242:109107. https://doi.org/10.1016/j.clim.2022.109107.

[37] Balmant BD, Fonseca DC, Prudêncio APA, Rocha IM, Callado L, Alves JTM, et al. Megamonas funiformis, plasma zonulin, and sodium intake affect C3 complement levels in inactive Systemic Lupus Erythematosus. Nutrients 2023:15. https://doi.org/10.3390/nu15081999.

[38] Gronke K, Nguyen M, Fuhrmann H, Santamaria De Souza N, Schumacher J, Pereira MS, et al. Translocating gut pathobiont *Enterococcus gallinarum* induces T_H17 and IgG3 anti-RNA–directed autoimmunity in mouse and human. Sci Transl Med 2025;17:eadj6294. https://doi.org/10.1126/scitranslmed.adj6294.

[39] Fine RL, Manfredo Vieira S, Gilmore MS, Kriegel MA. Mechanisms and consequences of gut commensal translocation in chronic diseases. Gut Microbes 2020;11:217–30. https://doi.org/10.1080/19490976.2019.1629236.

[40] James W, Ogunrinde E, Wan Z, Kamen DL, Oates J, Gilkeson GS, et al. A distinct plasma microbiome but not gut microbiome in patients with systemic lupus erythematosus compared to healthy individuals. J Rheumatol 2022. https://doi.org/10.3899/jrheum.210952.

[41] Benckert J, Schmolka N, Kreschel C, Zoller MJ, Sturm A, Wiedenmann B, et al. The majority of intestinal IgA+ and IgG+ plasmablasts in the human gut are antigen-specific. J Clin Invest 2011;121:1946–55. https://doi.org/10.1172/JCI44447.

[42] Garabatos N, Santamaria P. Gut microbial antigenic mimicry in autoimmunity. Front Immunol 2022;13:873607. https://doi.org/10.3389/fimmu.2022.873607.

[43] Azzouz DF, Chen Z, Izmirly PM, Chen LA, Li Z, Zhang C, et al. Longitudinal gut microbiome analyses and blooms of pathogenic strains during lupus disease flares. Ann Rheum Dis 2023;82:1315–27. https://doi.org/10.1136/ard-2023-223929.

[44] Zhang S-X, Wang J, Chen J-W, Zhang M-X, Zhang Y-F, Hu F-Y, et al. The level of peripheral regulatory T cells is linked to changes in gut commensal microflora in patients with systemic lupus erythematosus. Ann Rheum Dis 2021;80:e177. https://doi.org/10.1136/annrheumdis-2019-216504.

[45] López P, de Paz B, Rodríguez-Carrio J, Hevia A, Sánchez B, Margolles A, et al. Th17 responses and natural IgM antibodies are related to gut microbiota composition in systemic lupus erythematosus patients. Sci Rep 2016:6. https://doi.org/10.1038/srep24072.

[46] Zegarra-Ruiz DF, El Beidaq A, Iñiguez AJ, Lubrano Di Ricco M, Manfredo Vieira S, Ruff WE, et al. A diet-sensitive commensal lactobacillus strain mediates TLR7-dependent systemic autoimmunity. Cell Host Microbe 2019;25:113–127.e6. https://doi.org/10.1016/j.chom.2018.11.009.

[47] Dekkers KF, Sayols-Baixeras S, Baldanzi G, Nowak C, Hammar U, Nguyen D, et al. An online atlas of human plasma metabolite signatures of gut microbiome composition. Nat Commun 2022;13:5370. https://doi.org/10.1038/s41467-022-33050-0.
[48] Idborg H, Oke V. Cytokines as biomarkers in systemic lupus erythematosus: value for diagnosis and drug therapy. Int J Mol Sci 2021;22:11327. https://doi.org/10.3390/ijms222111327.
[49] Ramos-Martínez I, Ramos-Martínez E, Cerbón M, Pérez-Torres A, Pérez-Campos Mayoral L, Hernández-Huerta MT, et al. The role of B cell and T cell glycosylation in systemic lupus erythematosus. Int J Mol Sci 2023;24:863. https://doi.org/10.3390/ijms24010863.
[50] He J, Chan T, Hong X, Zheng F, Zhu C, Yin L, et al. Microbiome and metabolome analyses reveal the disruption of lipid metabolism in systemic lupus erythematosus. Front Immunol 2020;11:1703. https://doi.org/10.3389/fimmu.2020.01703.
[51] Brown J, Robusto B, Morel L. Intestinal dysbiosis and tryptophan metabolism in autoimmunity. Front Immunol 2020;11:1741. https://doi.org/10.3389/fimmu.2020.01741.
[52] Rodríguez-Carrio J, Alperi-López M, López P, Ballina-García FJ, Suárez A. Non-esterified fatty acids profiling in rheumatoid arthritis: associations with clinical features and Th1 response. PLoS One 2016;11:e0159573. https://doi.org/10.1371/journal.pone.0159573.
[53] González S, Gutie Rrez-Díaz I, Lo Pez P, Suárez A, Fernández-Navarro T, Sánchez B, et al. Microbiota and oxidant-antioxidant balance in systemic lupus erythematosus. Nutr Hosp 2017;34:934–41. https://doi.org/10.20960/nh.546.
[54] Widhani A, Djauzi S, Suyatna FD, Dewi BE. Changes in gut microbiota and systemic inflammation after synbiotic supplementation in patients with systemic lupus erythematosus: a randomized, double-blind, placebo-controlled trial. Cells 2022:11. https://doi.org/10.3390/cells11213419.
[55] Anders H-J, Saxena R, Zhao M, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nat Rev Dis Primers 2020;6:7. https://doi.org/10.1038/s41572-019-0141-9.
[56] Cornet A, Andersen J, Myllys K, Edwards A, Arnaud L. Living with systemic lupus erythematosus in 2020: a European patient survey. Lupus Sci Med 2021;8:e000469. https://doi.org/10.1136/lupus-2020-000469.
[57] Crost EH, Coletto E, Bell A, Juge N. *Ruminococcus gnavus*: friend or foe for human health. FEMS Microbiol Rev 2023;47:fuad014. https://doi.org/10.1093/femsre/fuad014.
[58] Carrión-Barberà I, Salman-Monte TC, Vílchez-Oya F, Monfort J. Neuropsychiatric involvement in systemic lupus erythematosus: A review. Autoimmun Rev 2021;20:102780. https://doi.org/10.1016/j.autrev.2021.102780.
[59] Cornet A, Karakikla Mitsakou Z, Andersen J, Dyball S, Chotai R, Sluijmers A, et al. Experiences and unmet needs of persons living with systemic lupus erythematosus in Europe: Lupus Europe's 2024 Swiss knife survey. Autoimmun Rev 2025;24:103838. https://doi.org/10.1016/j.autrev.2025.103838.
[60] Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, van Vollenhoven R, et al. Systemic lupus erythematosus. Nat Rev Dis Primers 2016;2:16039. https://doi.org/10.1038/nrdp.2016.39.
[61] Vich Vila A, Collij V, Sanna S, Sinha T, Imhann F, Bourgonje AR, et al. Impact of commonly used drugs on the composition and metabolic function of the gut microbiota. Nat Commun 2020;11:362. https://doi.org/10.1038/s41467-019-14177-z.
[62] Chen J, Wright K, Davis JM, Jeraldo P, Marietta EV, Murray J, et al. An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. Genome Med 2016;8:43. https://doi.org/10.1186/s13073-016-0299-7.
[63] Pan Z-Y, Chang Y-X, Han N, Hou F-Y, Lee BJY, Zhi F-C, et al. Short-term high-dose gavage of hydroxychloroquine changes gut microbiota but not the intestinal integrity and immunological responses in mice. Life Sci 2021;264:118450. https://doi.org/10.1016/j.lfs.2020.118450.
[64] Imhann F, Vich Vila A, Bonder MJ, Lopez Manosalva AG, Koonen DPY, Fu J, et al. The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. Gut Microbes 2017;8:351–8. https://doi.org/10.1080/19490976.2017.1284732.
[65] He Z, Kong X, Shao T, Zhang Y, Wen C. Alterations of the gut microbiota associated with promoting efficacy of prednisone by bromofuranone in MRL/lpr mice. Front Microbiol 2019;10:978. https://doi.org/10.3389/fmicb.2019.00978.
[66] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559–63. https://doi.org/10.1038/nature12820.
[67] Islam MA, Khandker SS, Kotyla PJ, Hassan R. Immunomodulatory effects of diet and nutrients in Systemic Lupus Erythematosus (SLE): a systematic review. Front Immunol 2020;11:1477. https://doi.org/10.3389/fimmu.2020.01477.
[68] Jiao H, Acar G, Robinson GA, Ciurtin C, Jury EC, Kalea AZ. Diet and systemic Lupus Erythematosus (SLE): from supplementation to intervention. Int J Environ Res Public Health 2022;19:11895. https://doi.org/10.3390/ijerph191911895.
[69] Cuervo A, Hevia A, López P, Suárez A, Sánchez B, Margolles A, et al. Association of polyphenols from oranges and apples with specific intestinal microorganisms in systemic lupus erythematosus patients. Nutrients 2015;7:1301–17. https://doi.org/10.3390/nu7021301.
[70] Huang C, Yi P, Zhu M, Zhou W, Zhang B, Yi X, et al. Safety and efficacy of fecal microbiota transplantation for treatment of systemic lupus erythematosus: an EXPLORER trial. J Autoimmun 2022;130:102844. https://doi.org/10.1016/j.jaut.2022.102844.
[71] Zheng M, Zhou W, Huang C, Hu Z, Zhang B, Lu Q, et al. A single-cell map of peripheral alterations after FMT treatment in patients with systemic lupus erythematosus. J Autoimmun 2023;135:102989. https://doi.org/10.1016/j.jaut.2022.102989.
[72] Zhang B, Zhou W, Liu Q, Huang C, Hu Z, Zheng M, et al. Effects of fecal microbiota transplant on DNA methylation in patients with systemic lupus erythematosus. J Autoimmun 2023:103047. https://doi.org/10.1016/j.jaut.2023.103047.
[73] Luo XM, Edwards MR, Mu Q, Yu Y, Vieson MD, Reilly CM, et al. Gut microbiota in human systemic lupus erythematosus and a mouse model of lupus. Appl Environ Microbiol 2017:84. https://doi.org/10.1128/AEM.02288-17.
[74] Wright EK, Kamm MA, Teo SM, Inouye M, Wagner J, Kirkwood CD. Recent advances in characterizing the gastrointestinal microbiome in Crohn's disease: a systematic review. Inflamm Bowel Dis 2015:1. https://doi.org/10.1097/MIB.0000000000000382.
[75] Zhou X, Nardini C. A method for automated pathogenic content estimation with application to rheumatoid arthritis. BMC Syst Biol 2016;10:107. https://doi.org/10.1186/s12918-016-0344-6.
[76] Breban M, Tap J, Leboime A, Said-Nahal R, Langella P, Chiocchia G, et al. Faecal microbiota study reveals specific dysbiosis in spondyloarthritis. Ann Rheum Dis 2017;76:1614–22. https://doi.org/10.1136/annrheumdis-2016-211064.
[77] Lee J-Y, Mannaa M, Kim Y, Kim J, Kim G-T, Seo Y-S. Comparative analysis of fecal microbiota composition between rheumatoid arthritis and osteoarthritis patients. Genes 2019;10:748. https://doi.org/10.3390/genes10100748.
[78] Bolte LA, Vich Vila A, Imhann F, Collij V, Gacesa R, Peters V, et al. Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. Gut 2021;70:1287–98. https://doi.org/10.1136/gutjnl-2020-322670.
[79] Singh RK, Chang H-W, Yan D, Lee KM, Ucmak D, Wong K, et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med 2017;15:73. https://doi.org/10.1186/s12967-017-1175-y.
[80] Ma Y, Xu X, Li M, Cai J, Wei Q, Niu H. Gut microbiota promote the inflammatory response in the pathogenesis of systemic lupus erythematosus. Mol Med Camb Mass 2019;25:35. https://doi.org/10.1186/s10020-019-0102-5.
[81] Xiang K, Wang P, Xu Z, Hu Y-Q, He Y-S, Chen Y, et al. Causal effects of gut microbiome on systemic lupus erythematosus: a two-sample mendelian randomization study. Front Immunol 2021;12:667097. https://doi.org/10.3389/fimmu.2021.667097.
[82] Xu Q, Ni J-J, Han B-X, Yan S-S, Wei X-T, Feng G-J, et al. Causal relationship between gut microbiota and autoimmune diseases: a two-sample mendelian randomization study. Front Immunol 2021;12:746998. https://doi.org/10.3389/fimmu.2021.746998.
[83] Manfredo Vieira S, Hiltensperger M, Kumar V, Zegarra-Ruiz D, Dehner C, Khan N, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science 2018;359:1156–61. https://doi.org/10.1126/science.aar7201.
[84] Tomofuji Y, Kishikawa T, Maeda Y, Ogawa K, Nii T, Okuno T, et al. Whole gut virome analysis of 476 Japanese revealed a link between phage and autoimmune disease. Ann Rheum Dis 2022;81:278–88. https://doi.org/10.1136/annrheumdis-2021-221267.
[85] Silverman GJ, Deng J, Azzouz DF. Sex-dependent Lupus Blautia (Ruminococcus) gnavus strain induction of zonulin-mediated intestinal permeability and autoimmunity. Front Immunol 2022;13:897971. https://doi.org/10.3389/fimmu.2022.897971.
[86] Katz-Agranov N, Zandman-Goddard G. The microbiome links between aging and lupus. Autoimmun Rev 2021;20:102765. https://doi.org/10.1016/j.autrev.2021.102765.
[87] Zhou H, Balint D, Shi Q, Vartanian T, Kriegel MA, Brito I. Lupus and inflammatory bowel disease share a common set of microbiome features distinct from other autoimmune disorders. Ann Rheum Dis 2025;84:93–105. https://doi.org/10.1136/ard-2024-225829.
[88] Bagavant H, Araszkiewicz AM, Ingram JK, Cizio K, Merrill JT, Arriens C, et al. Immune response to *Enterococcus gallinarum* in lupus patients is associated with a subset of lupus-associated autoantibodies. Front Immunol 2021;12:635072. https://doi.org/10.3389/fimmu.2021.635072.
[89] Shamriz O, Mizrahi H, Werbner M, Shoenfeld Y, Avni O, Koren O. Microbiota at the crossroads of autoimmunity. Autoimmun Rev 2016;15:859–69. https://doi.org/10.1016/j.autrev.2016.07.012.
[90] Li B-Z, Wang H, Li X-B, Zhang Q-R, Huang R-G, Wu H, et al. Altered gut fungi in systemic lupus erythematosus - A pilot study. Front Microbiol 2022;13:1031079. https://doi.org/10.3389/fmicb.2022.1031079.
[91] Yang P, Xu R, Chen F, Chen S, Khan A, Li L, et al. Fungal gut microbiota dysbiosis in systemic lupus erythematosus. Front Microbiol 2023;14:1149311. https://doi.org/10.3389/fmicb.2023.1149311.
[92] Chen C, Yan Q, Yao X, Li S, Lv Q, Wang G, et al. Alterations of the gut virome in patients with systemic lupus erythematosus. Front Immunol 2022;13:1050895. https://doi.org/10.3389/fimmu.2022.1050895.

Glossary

Alpha Diversity: A measure of microbial richness and evenness within an individual's gut microbiome, often reduced in disease states.
Beta Diversity: A measure comparing microbial composition between individuals or groups, highlighting differences in community structure.
Dysbiosis: An imbalance in the composition and function of the gut microbiota, often linked to disease states.
Fecal Microbiota Transplantation (FMT): The transfer of stool from a healthy donor to a patient to restore gut microbiota balance.
Firmicutes/Bacteroidetes Ratio (F/B ratio): A commonly used marker of gut microbial composition, taking into account the relative abundance of two of the most prevalent phyla, with alterations associated with dysbiosis and various diseases, including SLE.

Glycan: A molecule composed of polysaccharides found in bacterial cell walls, involved in immune system interactions and inflammation.

Gut Microbiome: The collection of microorganisms, including bacteria, fungi, and viruses, that inhabit the gastrointestinal tract.

Intestinal Permeability: The ability of the gut lining to regulate the passage of substances; increased permeability ("leaky gut") may contribute to immune activation.

Mendelian Randomization: A method that uses genetic variants associated with a risk factor as tools to determine whether the risk factor has a causal effect on a disease, helping to reduce confounding and reverse causation.

Microbiome-Based Therapeutics: Treatments that target the gut microbiota, such as probiotics, prebiotics, dietary interventions, and FMT.

Molecular Mimicry: A process where bacterial antigens resemble host proteins, potentially triggering autoimmune responses.

Pathobiont: A normally harmless microorganism in the gut microbiome that can become pathogenic under certain conditions, such as immune dysregulation or microbiota imbalance.

Short-Chain Fatty Acids (SCFAs): Metabolites produced by gut bacteria from dietary fibers, playing a key role in immune regulation and gut health.