

REVIEW ARTICLE

Microbial matchmakers: How microbiome dysbiosis fans the flames of chronic inflammation

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Abstract

The human gut microbiome plays a critical role in maintaining immune homeostasis and metabolic health. Aging is accompanied by significant shifts in microbial composition—termed dysbiosis—which contribute to a proinflammatory state known as “inflammaging.” This chronic, low-grade inflammation underlies numerous age-associated diseases, including atherosclerosis, neurodegeneration, and metabolic syndrome. This review aims to explore the mechanisms through which age-related microbial dysbiosis contributes to chronic inflammation and to examine current therapeutic strategies targeting the microbiome to mitigate inflammaging. A comprehensive literature review was conducted using PubMed-indexed articles from 2000 to 2025. Studies addressing microbiome composition in aging, microbial metabolite pathways, immune modulation, and interventions including probiotics, dietary modifications, and fecal microbiota transplantation (FMT) were included. Aging is associated with reduced microbial diversity, a decline in beneficial taxa such as *Faecalibacterium prausnitzii*, and enrichment of proinflammatory taxa like *Proteobacteria*. This dysbiosis impairs gut barrier function, promoting systemic translocation of microbial products such as lipopolysaccharide (LPS). Metabolites like short-chain fatty acids (SCFAs) are diminished, leading to decreased regulatory T cell (Treg) function and epithelial integrity. Conversely, elevated levels of trimethylamine N-oxide (TMAO) and LPS activate pattern recognition receptors, triggering innate immune pathways (e.g., NF-κB, NLRP3 inflammasome) that perpetuate chronic inflammation. Interventions such as probiotic supplementation and FMT from young donors show promise in reversing dysbiosis, restoring microbial metabolites, and attenuating inflammatory responses in both animal models and early human trials. Understanding the gut-immune-metabolite axis offers new opportunities to intervene in age-related diseases through targeted microbiome modulation.

Keywords: Microbiome; Inflammaging; Dysbiosis; Short-chain fatty acids; Trimethylamine N-oxide; Lipopolysaccharide

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1. Introduction

Aging is accompanied by a chronic, low-grade, sterile inflammatory state termed “inflammaging,” characterized by elevated levels of proinflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α), and C-reactive protein (CRP) in the absence of overt infection.¹ This persistent inflammation is a significant risk factor for morbidity and mortality in the elderly, contributing to the pathogenesis of various age-related diseases, including cardiovascular disorders, neurodegenerative conditions, and metabolic syndromes.^{2,3}

The gut microbiome, a complex and dynamic community of microorganisms residing in the gastrointestinal tract, plays a pivotal role in maintaining immune homeostasis.^{1,4} It influences the development and function of both innate and adaptive immune responses through the production of microbial metabolites, modulation of immune cell differentiation, and maintenance of the intestinal barrier integrity.⁵ A balanced gut microbiota promotes the differentiation of regulatory T cells (Tregs) and the production of anti-inflammatory cytokines, thereby

supporting immune tolerance and preventing excessive inflammatory responses (Figure 1).⁵

Dysbiosis, defined as an imbalance in the composition and function of the gut microbiota, disrupts this equilibrium and is associated with increased intestinal permeability, commonly referred to as “leaky gut.”^{6,7} This condition allows translocation of microbial products such as lipopolysaccharide (LPS) into the systemic circulation, triggering immune activation through pattern recognition receptors like Toll-like receptor 4 (TLR4) and promoting chronic inflammation.⁶ Age-related changes in the gut microbiota, including reduced diversity and a decline in beneficial commensals, exacerbate this proinflammatory milieu, contributing to the progression of inflammaging.^{2,8}

This review explores how microbiome dysbiosis acts as a “matchmaker” in sustaining chronic inflammation during aging. We examine the mechanisms by which alterations in the gut microbiota influence immune regulation and contribute to inflammaging, and discuss potential therapeutic strategies aimed at restoring microbial balance to mitigate age-associated inflammatory conditions.^{1,2,5,6,9}

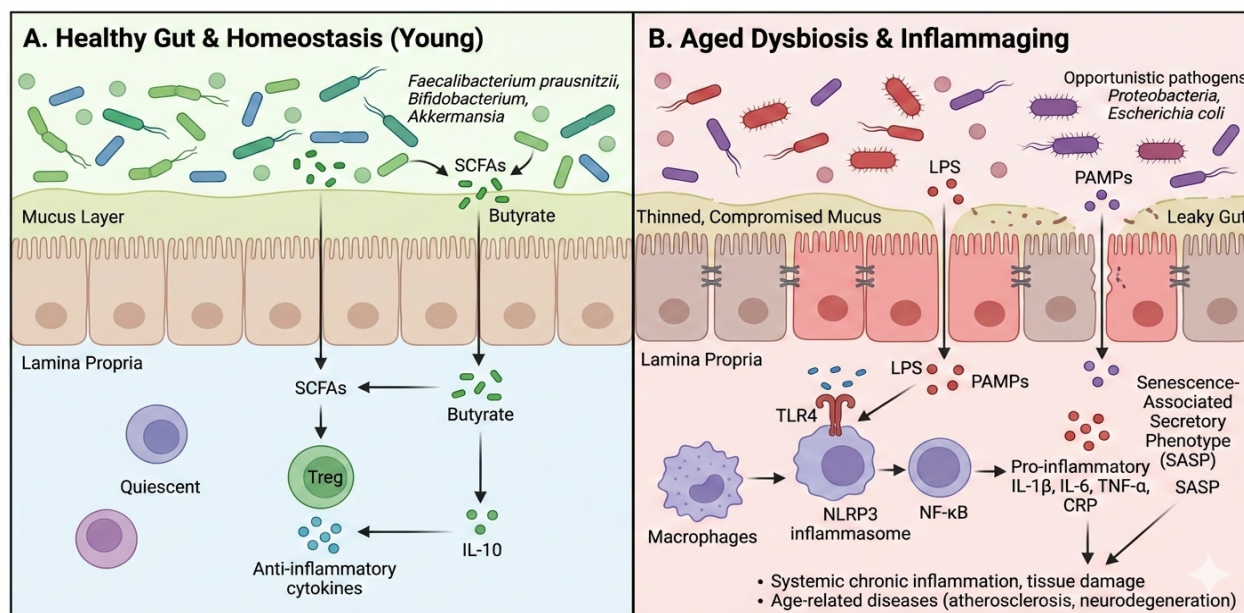


Figure 1. The gut–inflammaging axis: homeostasis vs. age-related dysbiosis. This schematic compares the intestinal environment of a healthy young individual (A) with that of an aging individual experiencing dysbiosis (B). Panel (A) highlights a robust mucus layer and tight epithelial junctions supported by beneficial taxa (e.g., *Faecalibacterium prausnitzii*, *Akkermansia*). These microbes produce SCFAs like butyrate, which promote Treg differentiation and an anti-inflammatory cytokine profile (e.g., IL-10). Panel (B) illustrates the “leaky gut” phenomenon where a thinned mucus layer and compromised tight junctions allow for the translocation of PAMPs and LPS. This triggers systemic inflammaging via the activation of macrophages, the NLRP3 inflammasome, and the NF- κ B pathway, exacerbated by the SASP and an increase in opportunistic pathogens like *Proteobacteria* and *E. coli*. Image created by the authors. Abbreviations: CRP: C-reactive protein; IL: Interleukin; LPS: Lipopolysaccharide; NF- κ B: Nuclear factor kappa B; PAMPs: Pathogen-associated molecular patterns; SASP: Senescence-associated secretory phenotype; SCFAs: Short-chain fatty acids; TLR4: Toll-like receptor 4; TNF- α : Tumor necrosis factor alpha; Treg: Regulatory T cell.

2. The gut microbiome and immune system crosstalk

The gut microbiome plays a pivotal role in modulating the host immune system, influencing both innate and adaptive immune responses (Figure 2).^{1,4,10,11} Key microbial taxa and their metabolites are integral to maintaining immune homeostasis, and disruptions in this balance can lead to chronic inflammation, particularly in the aging population.^{2,11}

2.1. Key microbial players

The human gut microbiota is predominantly composed of the phyla Firmicutes and Bacteroidetes, with notable contributions from Verrucomicrobia, particularly *Akkermansia muciniphila*.^{8,12} Firmicutes, including genera such as *Clostridium* and *Lactobacillus*, are known for producing short-chain fatty acids (SCFAs) like butyrate, which have anti-inflammatory properties.⁵ Bacteroidetes, including *Bacteroides* species, contribute to the fermentation of complex carbohydrates and also produce SCFAs.⁵ *Akkermansia muciniphila*, a mucin-degrading

bacterium, has been associated with enhanced gut barrier function and modulation of immune responses.⁶ Recent evidence highlights the role of interspecies interactions in controlling *Escherichia coli* growth; the loss of microbial diversity in aging reduces these inhibitory interactions, permitting the overgrowth of such opportunistic pathobionts.¹³

2.2. Microbial metabolites and immune effects

Microbial metabolites such as SCFAs, LPS, and trimethylamine *N*-oxide (TMAO) significantly influence immune function.

SCFAs. Produced through the fermentation of dietary fibers by gut bacteria, SCFAs—including acetate, propionate, and butyrate—serve as energy sources for colonocytes and regulate immune responses. Butyrate, in particular, promotes the differentiation of Tregs and suppresses proinflammatory cytokine production, thereby maintaining intestinal homeostasis.^{5,14}

LPS. A component of the outer membrane of Gram-negative bacteria, LPS can translocate into the systemic

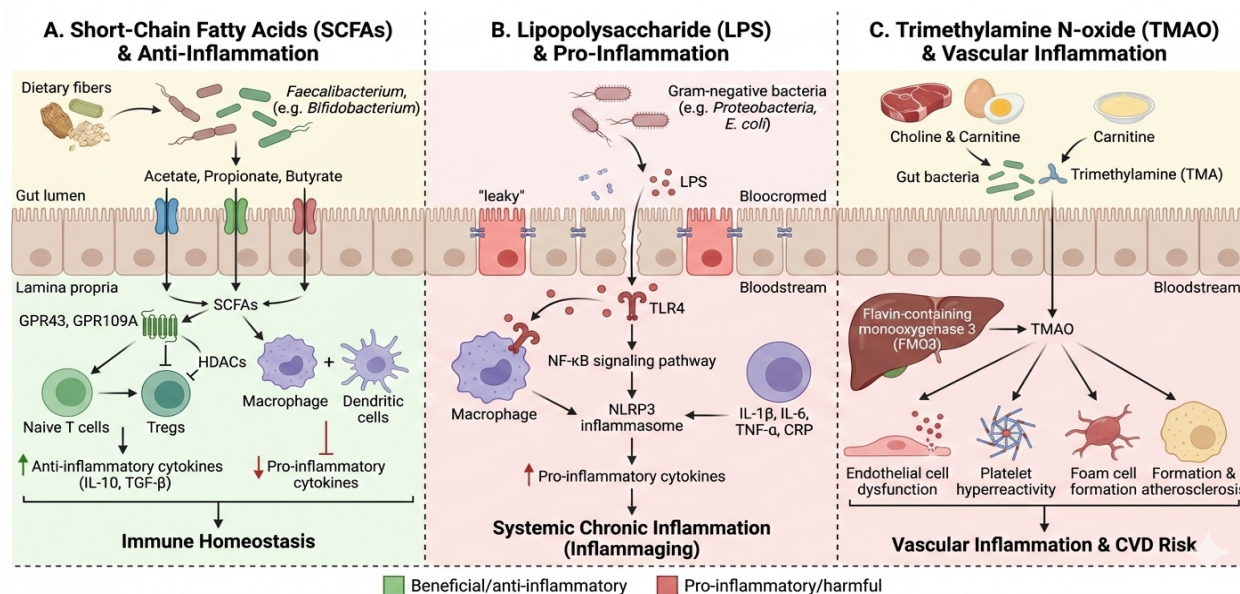


Figure 2. Host immunity-modulating pathways influenced by key microbial metabolites. (A) Beneficial SCFAs bind to GPCRs to suppress proinflammatory NF-κB signaling and enhance gut barrier integrity. (B) LPS translocates across the epithelium to bind with TLR4. The figure highlights the age-related upregulation of TLR4 expression and the hypersensitivity of downstream cascades that lead to the overproduction of IL-6 and TNF-α. (C) The pathway of TMAO production from dietary precursors is traced plays a role in promoting vascular inflammation and oxidative stress through NLRP3 inflammasome activation. Image created by the authors.

Abbreviations: CRP: C-reactive protein; CVD: Cardiovascular disease; GPCRs: G-protein coupled receptors; HDACs: Histone deacetylases; IL: Interleukin; LPS: Lipopolysaccharide; NF-κB: Nuclear factor kappa B; PAMPs: Pathogen-associated molecular patterns; SCFAs: Short-chain fatty acids; TGF-β: Transforming growth factor beta; TLR4: Toll-like receptor 4; TMAO: Trimethylamine *N*-oxide; TNF-α: Tumor necrosis factor alpha; Treg: Regulatory T cell.

circulation when the gut barrier is compromised. This translocation activates TLR4 on immune cells, leading to the production of proinflammatory cytokines and contributing to systemic inflammation.^{6,15}

TMAO. Derived from the microbial metabolism of dietary choline and carnitine, TMAO has been implicated in promoting atherosclerosis by influencing cholesterol metabolism and enhancing inflammatory responses.⁹

2.3. Gut barrier integrity: Intrinsic and extrinsic factors

The maintenance of the intestinal barrier is a dynamic process involving a complex interplay between the mucus layer, tight junction proteins such as occludin and zonulin, and the underlying immune epithelium. While biological aging inherently shifts the gut toward a more permeable state—a phenomenon often termed “leaky gut”—this integrity is profoundly influenced by extrinsic factors common in older populations.^{2,6} Nutritional habits, particularly high-fat diets (HFD) prevalent in Western societies, drive the expansion of bile-tolerant, proinflammatory bacteria that degrade the protective mucus layer. This microbial shift leads to a reduction in tight junction protein expression, facilitating the paracellular translocation of LPS. In older adults, the consumption of a diet low in fermentable fibers further starves beneficial butyrate-producing taxa, depriving colonocytes of their primary energy source and leading to epithelial atrophy.^{2,6,7}

Furthermore, the high “medication burden” typical of older adults directly exacerbates barrier dysfunction independently of chronological age. Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) for managing age-related conditions induces “NSAID-enteropathy” by inhibiting prostaglandin synthesis, which is vital for mucosal blood flow and bicarbonate secretion. Similarly, the frequent use of proton pump inhibitors (PPIs) alters the gastric pH barrier, allowing oral and upper-respiratory bacteria to colonize the lower gastrointestinal tract, often leading to small intestinal bacterial overgrowth (SIBO) and localized inflammation. Coupled with frequent antibiotic cycles that deplete protective species, these extrinsic clinical exposures act as cumulative stressors that compromise the epithelial seal, suggesting that “leaky gut” in the elderly is as much a result of environmental and medical history as it is a consequence of biological aging.^{1,2,5,6,9}

3. Mechanisms linking dysbiosis to chronic inflammation

The relationship between gut microbiome dysbiosis and chronic inflammation is multifaceted, involving immune

activation, microbial translocation, metabolic imbalances, and cellular senescence, all of which contribute to the sustained proinflammatory milieu observed in aging and related diseases.^{1,2,6,13} Dysbiosis disrupts the balanced interaction between host immune receptors and microbial components, leading to aberrant immune activation. Pattern recognition receptors (PRRs), such as TLRs and the NLRP3 inflammasome, recognize microbial-associated molecular patterns (MAMPs) from dysbiotic communities. Overactivation of TLRs—especially TLR4 by LPS—triggers downstream signaling, including nuclear factor kappa B (NF- κ B), promoting proinflammatory cytokine production.^{6,16} The NLRP3 inflammasome senses cellular stress and microbial danger signals, leading to caspase 1 activation and secretion of IL-1 β and IL-18.¹³ Critically, aging is associated with shifts in TLR4 sensitivity rather than just expression levels; aged immune cells may exhibit persistent low-level signaling or an inability to downregulate NF- κ B pathways once triggered by translocated LPS.

A hallmark of dysbiosis-associated inflammation is increased intestinal permeability (“leaky gut”), allowing translocation of microbial components such as LPS into systemic circulation, causing metabolic endotoxemia.^{6,7} Dysbiosis often reduces beneficial SCFAs like butyrate, acetate, and propionate, which maintain intestinal epithelial integrity and suppress inflammatory pathways.^{5,14} Conversely, dysbiosis elevates proinflammatory metabolites such as TMAO, linked to vascular inflammation and atherosclerosis.^{9,17}

Cellular senescence, a hallmark of aging, involves permanent cell cycle arrest and the secretion of proinflammatory cytokines, chemokines, and proteases. Emerging evidence indicates microbial dysbiosis can exacerbate senescence-associated secretory phenotype (SASP), partly through chronic immune activation and metabolic alterations^{2,13,7}, creating a feedback loop that sustains inflammation.

4. Evidence from human and animal studies

The intricate relationship between aging, microbiome alterations, and chronic inflammation—commonly termed inflammaging—has been extensively studied using both human cohorts and animal models. These studies provide compelling evidence that aging-associated shifts in the gut microbiome contribute significantly to systemic inflammation. In humans, aging is characterized by a decline in gut microbiome diversity and stability, with notable reductions in beneficial taxa such as *Bifidobacterium* and *Faecalibacterium prausnitzii*,

alongside expansions of potentially pathogenic bacteria, including members of the Proteobacteria phylum.¹ These dysbiotic changes impair metabolic functions such as SCFA production and compromise mucosal barrier integrity, promoting inflammatory processes. Similar observations have been made in aged rodents, where aging correlates with decreased microbial richness and increased proinflammatory bacterial populations.¹³ Such dysbiosis is implicated in frailty, metabolic disturbances, and immune dysfunction. Elevated systemic levels of proinflammatory cytokines including IL-6, TNF- α , and C-reactive protein (CRP) serve as robust biomarkers of inflammaging.

Human studies reveal strong correlations between these biomarkers and gut microbiome alterations, especially in elderly populations exhibiting reduced microbial diversity and increased gut permeability.² Longitudinal cohort data show that elevated IL-6 and CRP levels are predictive of morbidity and mortality in older adults and are tightly linked to microbiome-mediated endotoxemia.³ In animal models, microbiome dysbiosis induces systemic inflammation characterized by heightened IL-6 and TNF- α production, mirroring human inflammaging profiles.^{6,18} Germ-free (GF) animal models have played a crucial role in clarifying how the gut microbiome contributes to inflammaging. GF mice consistently show reduced basal inflammation and diminished expression of age-related inflammatory markers when compared with conventionally colonized mice, suggesting that microbial signals are necessary for the full activation of age-associated immune pathways. Experimental observations further reveal that introducing an aged or dysbiotic microbial community into susceptible hosts disrupts gut barrier integrity, increases intestinal permeability, and elevates systemic proinflammatory cytokines—changes that mirror key characteristics of inflammaging. These results underscore the causal role of microbiome composition in shaping immune responses during aging and highlight the importance of microbial balance in maintaining epithelial and systemic homeostasis.⁶ While fecal microbiota transplantation (FMT) from young to aged mice can successfully rejuvenate the intestinal landscape and reduce systemic inflammation, these effects are predominantly transient. Longitudinal evaluations in rodent models indicate that the “young” microbial profile and its associated anti-inflammatory benefits typically diminish unless supported by continuous dietary interventions or repeated administrations. Furthermore, we clarify that the success of these studies—and their potential translation to humans—relies on rigorous donor criteria, defining “healthy young donors” as those within a specific age range (18–30) with optimal metabolic health and a lack of proinflammatory microbial signatures.

5. Therapeutic interventions targeting the microbiome

The recognition of the gut microbiome's key role in inflammaging has intensified efforts to develop interventions that restore microbial balance in older adults.¹⁰ These approaches include probiotics, FMT, targeted dietary patterns, and pharmacological strategies that consider microbiome–drug interactions.⁴

Probiotics, which consist of live beneficial microorganisms, have been shown to support gut barrier integrity and enhance immune regulation in aging populations.¹⁹ Specific effective regimens in aging populations include *Bifidobacterium animalis* subsp. *lactis* HN019 (10⁹ CFU/day for 3–6 weeks) and *Lactobacillus rhamnosus* GG, which have shown the greatest effectiveness in improving barrier function and immune markers. Benefits generally persist during the intervention but may decline within weeks of discontinuation, highlighting the need for consistent supplementation. They also reduce proinflammatory cytokines such as IL-6 and TNF- α in experimental and clinical studies.²⁰ Prebiotics, which selectively promote the growth of beneficial taxa, further contribute to improved gut homeostasis by enriching SCFA-producing microbes.⁵ Synbiotics, combining probiotics and prebiotics, enhance microbial colonization and metabolic activity and have been associated with improvements in inflammation and metabolic function in older adults (Figure 3).²¹

FMT has emerged as a promising strategy for reversing age-related dysbiosis by transferring microbiota from healthy donors to individuals with disrupted microbial communities.⁶ Preclinical studies show that FMT can restore microbial diversity, strengthen gut epithelial integrity, and reduce systemic inflammation in aged models.⁷ FMT from young donors can restore diversity in aged models. “Healthy young donors” are typically defined as individuals aged 18–30 with a healthy body mass index, no history of gastrointestinal or metabolic disorders, and recent screening for multidrug-resistant organisms. However, risks in older adults include procedural complications and the ethical concern of introducing latent microbial traits into a fragile host. Early clinical findings in older adults also indicate improved microbial profiles following FMT, though large controlled trials are still needed to establish long-term efficacy and safety.²²

Dietary modulation remains one of the most effective strategies for improving gut microbiome composition across the lifespan.²³ High-fiber diets increase SCFA production, strengthen gut barrier function, and reduce low-grade inflammation—a hallmark of inflammaging.²⁴

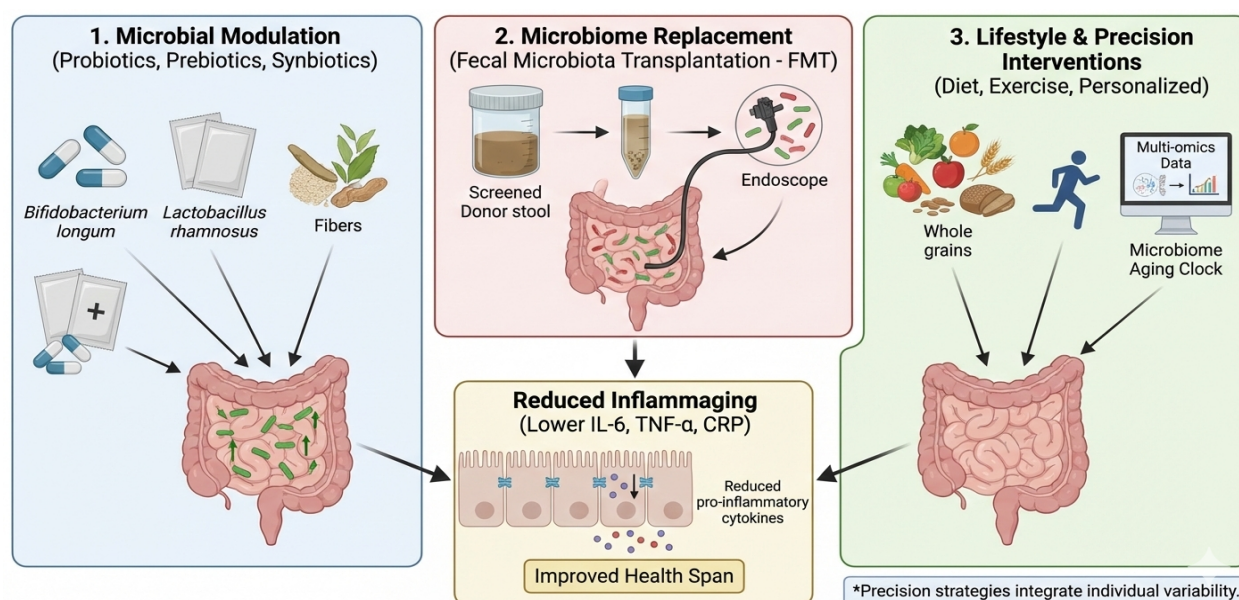


Figure 3. Current and emerging interventions aimed at mitigating chronic inflammation. Panel (1): Microbial modulation using probiotics, prebiotics, and synbiotics refers to the administration of specific strains (e.g., *Bifidobacterium longum*) and fibers to restore microbial diversity and SCFA production. Panel (2): Fecal microbiota transplantation (FMT) refers to an approach that transfers a healthy “young” microbiome to an aged host to reset the gut ecosystem, while noting the transient nature of these effects without lifestyle support. Panel (3): Lifestyle and precision interventions involves the integration of multi-omics data (metagenomics/metabolomics) with extrinsic factors—such as moderate physical activity and caloric regulation—to create personalized therapeutic regimens tailored to an individual’s unique “microbiome clock.” Image created by the authors.

Abbreviations: CRP: C-reactive protein; IL: Interleukin; TNF- α : Tumor necrosis factor alpha.

Polyphenol-rich foods such as berries, green tea, and cocoa promote beneficial microbial species and suppress proinflammatory taxa through antioxidative and immunomodulatory mechanisms.²⁵

Pharmacomicrobiomics has gained increasing attention due to the high medication burden in aging populations.²⁶ Certain microbes can metabolize widely used drugs, altering their efficacy and side-effect profiles.²⁷ Conversely, medications can shift microbiome composition in ways that may worsen dysbiosis and inflammation, emphasizing the need to integrate microbiome considerations into personalized drug regimens for older adults.²⁸

In summary, while microbiome-targeted therapies like probiotics and FMT offer significant potential for mitigating inflammaging, their clinical efficacy is heavily contingent upon host lifestyle factors, particularly caloric intake and physical activity. Excessive caloric consumption promotes “meta-inflammation” and dysbiosis, whereas regular, moderate exercise strengthens the gut–muscle axis by enhancing the abundance of anti-inflammatory taxa and maintaining intestinal barrier integrity. Because these extrinsic factors independently modulate systemic immune tone and microbial composition, they serve as critical confounding variables; therefore, successful interventions

must transition toward precision strategies that integrate these lifestyle parameters to ensure sustained restoration of microbial homeostasis in the aging population.

6. Challenges and future directions

The promise of microbiome-targeted therapies in mitigating inflammaging is tempered by significant challenges that must be addressed to realize their full clinical potential.¹⁰ The complexity and individuality of the gut microbiome, together with its dynamic changes across the lifespan, demand personalized approaches supported by rigorous longitudinal research and reliable biomarkers.^{4,29}

One of the foremost challenges lies in the substantial heterogeneity of the aging microbiome across individuals, shaped by genetics, diet, lifestyle, medication use, and comorbidities.⁸ This variability limits the effectiveness of uniform interventions. Personalized microbiome therapies leveraging multi-omics data—such as metagenomics, metabolomics, and transcriptomics—show promise for tailoring microbial modulation to restore homeostasis and reduce inflammaging.³⁰ Machine learning and computational models are increasingly applied to predict individual responses to dietary and microbial interventions, offering a path toward precision treatment

strategies.³¹ However, implementing these approaches in clinical settings requires overcoming major technical, regulatory, and ethical challenges.¹⁰

Current knowledge of microbiome dynamics during aging is largely derived from cross-sectional studies, restricting causal interpretation of microbiome changes and the progression of inflammaging.¹ Longitudinal studies that track microbial composition, metabolic function, and host immune markers over time are essential for identifying critical windows for intervention and monitoring therapeutic responses.^{6,32} Standardization of sampling procedures, sequencing pipelines, and analytic methods remains crucial for ensuring reproducibility and comparability across research cohorts.³³

Emerging evidence highlights the utility of microbiome-based aging “clocks,” which estimate biological age and predict health trajectories based on microbial signatures associated with inflammation and aging.³¹ These clocks integrate functional and taxonomic features to serve as non-invasive biomarkers for inflammaging. However, improvements are needed to enhance their accuracy, population generalizability, and integration with other molecular aging metrics such as epigenetic and transcriptomic clocks.³⁴ Multi-dimensional biomarker platforms that combine microbiome data with host molecular profiles may ultimately provide a comprehensive framework for diagnosing and managing inflammaging.⁷

7. Conclusion

Aging is closely intertwined with progressive alterations in the gut microbiome that impair metabolic function, weaken epithelial barrier integrity, and promote the chronic low-grade inflammation characteristic of inflammaging. Evidence from both human cohorts and animal models demonstrates that dysbiosis contributes directly to immune activation, increased intestinal permeability, and heightened levels of inflammatory biomarkers. These microbiome-driven mechanisms not only accelerate physiological decline but also influence susceptibility to age-related diseases.

While therapeutic strategies such as probiotics, prebiotics, synbiotics, FMT, and dietary modulation offer promising avenues for reducing inflammatory burden, substantial challenges remain—most notably high inter-individual microbiome variability. To address this, future efforts must shift toward precision interventions that integrate multi-omics data to tailor treatments to an individual's unique microbial and inflammatory profile. Such approaches may involve combining personalized dietary regimens with specific probiotic strains and prebiotic fibers to maximize therapeutic efficacy and

ensure the long-term restoration of microbial homeostasis. Ultimately, a deeper understanding of the gut microbiome's role in inflammaging, supported by longitudinal data and reliable aging “clocks,” will be essential to translate these precision therapies into effective tools for extending health span and improving quality of life in aging populations.

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Conflict of interest

The authors declare they have no competing interests.

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Not applicable.

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