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REVIEW

The Gut Microbiota in Aging: From Compositional Shifts to Therapeutic Opportunities

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Abstract

Population aging is accelerating worldwide, creating an urgent need to understand biological processes that influence late-life health. The gut microbiota, defined here primarily as the bacterial communities inhabiting the intestine, changes across the lifespan and may contribute to immune, metabolic, neural, and musculoskeletal phenotypes of aging. However, reported age-related microbiota signatures remain heterogeneous, reflecting differences in cohort design, sequencing strategy, functional annotation, and clinical context. In this review, we synthesize evidence from human cohorts, animal models, and mechanistic studies on the bidirectional relationship between host aging and gut microbial remodeling. A central theme is that host factors such as immune senescence, barrier dysfunction, altered gastrointestinal physiology, and medication exposure can drive microbial change. In contrast, microbial products can feed back on aging tissues. We distinguish chronological aging, healthy aging, frailty, exceptional longevity, and age-related diseases, and we evaluate how diet, medication exposure, living environment, geography, and disease burden shape reported microbiota signatures. We further organize microbial functions around metabolite-centered pathways, including short-chain fatty acids (SCFAs), trimethylamine *N*-oxide (TMAO), phenylacetylglutamine (PAGln), bile acids, tryptophan derivatives, and uremic microbial toxins. This framework clarifies when microbial alterations should be interpreted as biomarkers, plausible mediators, or candidate therapeutic targets. Finally, we discuss microbiota-targeted interventions, including diet, prebiotics, probiotics, fecal microbiota transplantation (FMT) , postbiotics, metabolite-based therapeutics, and phage-based strategies, while emphasizing current limits in causal inference, safety, biomarker validation, and clinical implementation.

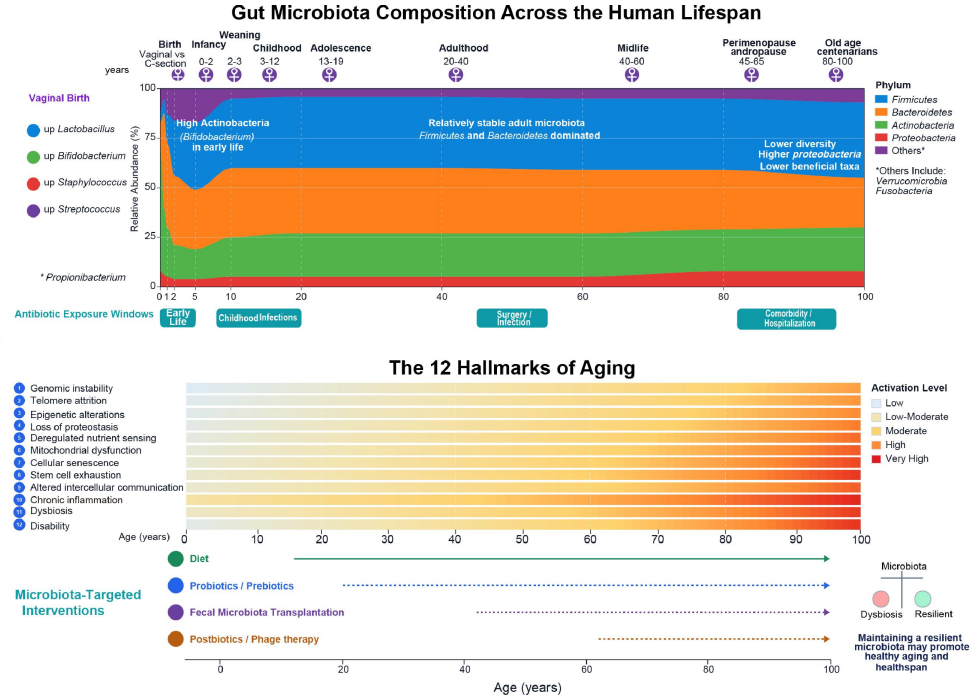
Keywords

Gut microbiota; Aging; Inflammaging; Short-chain fatty acids; Dysbiosis; Probiotics; Healthy aging

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Graphical Abstract



Highlights

- This review synthesizes human, animal, and mechanistic evidence on bidirectional host-microbiota remodeling during aging.
- It distinguishes chronological aging, healthy aging, frailty, exceptional longevity, and age-related diseases to refine microbiota signatures.
- It links metabolite-centered mechanisms with microbiota-targeted interventions while highlighting causal, safety, and clinical translation gaps.

1. Introduction

The global population is aging at a quicker rate than ever. It is estimated that by 2050[1], there will be over 2.10 billion people aged 60 years or older, which will be more than a fifth of the world population. With such a demographic change, there is also a greater burden of chronic, functional, and neurodegenerative diseases, which highlights the necessity to find modifiable biological systems that can sustain healthy longevity. López-Otín *et al.*[2] have described an extended set of interconnected hallmarks of aging, including chronic inflammation and dysbiosis. In this context, gut microbial imbalance can be considered a novel and potentially modifiable aspect of the biology of aging, instead of an already known and independent causative agent of human aging.

The process of aging also alters mucosal immunity by changing the ecological filters that are responsible for forming intestinal microbial communities. A recent pan-organ spatial transcriptomic study identified inflammatory immunoglobulin-related pathways in aged tissues[3], and experimental results suggest that compromised B cell activity and lack of immunoglobulin A (IgA) responses may impair the host's ability to control microorganisms in the gut[4]. Such findings can support a host-to-microbe aspect of aging: immunosenescence may decrease microbial containment, change antibody-mediated selection, and promote community drift or growth of pathobionts. Nevertheless, strategies of immune restoration like removal of immunoglobulin G (IgG) or transplantation of B cells cannot currently be included in the clinical evidence base of microbiota-targeted healthy aging.

Gut microbiota in this review refers to living microbial communities in the intestine, whereas the gut microbiome means their total genes, functions, and ecological environment. Since most existing aging researches relies on 16S rRNA gene sequencing or shotgun metagenomics analysis of fecal samples, this review focuses primarily on bacterial gut microbiota and its functional outcomes while acknowledging that the virome, mycobiome, and archaeome are significant but poorly studied elements. The human gut microbiota plays a role in digestion of nutrients, colonization-resistance, mucosal immune education, gut-brain and gut-distal organ signaling, and synthesis of bioactive metabolites including vitamins, amino-acid derivatives, secondary bile acids, and short-chain fatty acids (SCFAs)[5,6]. From early life onward, its composition is influenced by the mode of delivery, diet, environment, exposure to medications, health condition, and aging itself[7]. Such characteristics render the gut microbiota a possible mediator between the pathophysiology of the host, environmental insults, and age-related disorders, including metabolic syndrome and neurodegeneration[8].

The critical reviews, such as those conducted by Ghosh *et al.*[9], have confirmed the significance of the gut microbiome in healthy aging. Four approaches are used to develop this basis in the current review. To begin with, it clearly differentiates between chronological aging, healthy aging, frailty, exceptional longevity and disease-related aging, so that the entire older population is not considered biologically similar. Secondly, it adopts a bidirectional host-microbiota model in which the mechanisms of microbe-to-host and host-induced changes in the microbial ecosystem receive more attention. Thirdly, it puts microbial metabolites at the heart of the mechanistic paradigm that connects taxonomic changes to cellular and systemic pathways of aging. Fourthly, it assesses microbiota-targeted treatments from a translational perspective, considering evidence level, safety, clinical outcomes, and implementation challenges.

1.1 Literature Search and Selection Strategy

For this narrative review, we searched PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar for English-language publications from January 2010 to August 2026. Search terms included combinations of gut microbiota, gut microbiome, aging, healthy aging, longevity, frailty, sarcopenia, Alzheimer's disease (AD), Parkinson's disease (PD), osteoporosis, osteoarthritis, cardiometabolic disease, SCFAs, trimethylamine *N*-oxide (TMAO), bile acids, tryptophan metabolites, postbiotics, probiotics, prebiotics, fecal microbiota transplantation (FMT) , and phage therapy. Priority was given to human cohort studies, longitudinal studies, randomized or controlled interventions, systematic reviews/meta-analyses, and mechanistic animal or cellular studies that directly connected microbial taxa, microbial functions, or microbial metabolites with aging-related phenotypes. Studies summarized in **Tables 1-3** were manually selected to represent evidence diversity across population cohorts, mechanistic layers, and translational interventions; non-aging adult intervention studies were retained only when they provided mechanistic or translational information relevant to older populations.

Table 1. Key human studies on gut microbiota and aging (2015–2026)

Study	Design	Population/N	Age Range	Sequencing Method	Key Findings	PMID
Odamaki *et al*. 2016[10]	Cross-sectional lifespan cohort	Japan; 367 subjects	0–104	16S rRNA	Continuous remodeling across lifespan; age-related shift in *Bifidobacterium* dominance	27220822
Kong *et al*. 2016[11]	Cross-sectional cross-cohort longevity comparison	China and Italy; 168 + subjects	3–100	16S rRNA + metagenomics	Longevity-associated *Christensenellaceae* and *Clostridium* IV/XIVa enrichment	27676296
Biagi *et al*. 2016[12]	Cross-sectional extreme-longevity cohort	Italy; 71 subjects including centenarians	22–109	16S rRNA	Centenarian-enriched *Bifidobacterium* and *Christensenellaceae*; lower *Faecalibacterium*	27185560
Bian *et al*. 2017[13]	Cross-sectional healthy-aging comparison	China; 102 healthy aged plus young adults	24–94	16S rRNA	Healthy older adults showed microbiota features closer to young adults than frail aging phenotypes	28959739
Wang *et al*. 2015[14]	Cross-sectional centenarian-control cohort	China; 14 centenarians plus controls	94–108	16S rRNA	Centenarians showed enrichment of *Roseburia* and *Clostridium*-related OTUs with cohort-specific taxa	25839332
Haran *et al*. 2018[15]	Cross-sectional nursing-home cohort	USA; 172 nursing-home elders	65–100 +	16S rRNA	Microbiota associated with frailty, nutrition, physical location, and reduced diversity	29134939

NOTE: OTUs: operational taxonomic units; N: the total number of subjects.

Table 2. Microbiota-derived metabolites linking gut microbial remodeling to aging-related phenotypes

Metabolite Class	Sources/Pathway	Host Targets	Phenotypes	Evidence Base	References
SCFAs	*Faecalibacterium prausnitzii* (*F. prausnitzii*), *Roseburia* spp., *Eubacterium rectale*, *Coprococcus* spp., *Anaerostipes* spp., and *Bifidobacterium*	GPR41/GPR43/GRP109A, HDACs, epithelial tight junctions, Tregs	Barrier integrity, immunoregulation, insulin sensitivity, frailty and sarcopenia	Human associations, RCTs, animal and cellular studies	[16-27]
TMAO	*Enterobacteriaceae*, *Clostridiaceae*, and *Desulfovibrionaceae*	Platelets, endothelium, mitochondria, inflammatory signaling	Atherosclerosis, cardiometabolic risk, renal-muscle axis, oxidative stress	Human cohorts and mechanistic models	[28-33]
PAGln and Aromatic Amino-Acid Products	Proteolytic fermentation and aromatic amino-acid metabolism	Adrenergic signaling, AMPK-related mitochondrial and senescence pathways	Cardiovascular risk, cellular senescence, mitochondrial dysfunction	Metabolomics cohorts and experimental models	[32,34]
Secondary Bile Acids	Microbial bile-acid deconjugation and transformation	FXR, TGR5, lipid and glucose metabolism, immune signaling	Metabolic aging, inflammation, barrier and hepatic phenotypes	Mechanistic and translational studies	[35]
Tryptophan Derivatives and Uremic Toxins	Indole and p-cresol production by tryptophanase-positive *Enterobacteriaceae* and anaerobic *Clostridia*	AhR signaling, renal clearance, muscle mitochondrial and protein-homeostasis pathways	Inflammation, gut-brain signaling, renal-muscle dysfunction, sarcopenia risk	Cohort and mechanistic evidence	[25,32,36,37]
3-Phenyllactic Acid	Microbial aromatic-lactate metabolism in model systems	SKN-1/ATFS-1 mitochondrial stress-response pathway	Healthspan extension and stress resilience in *C. elegans*	Model-organism mechanistic evidence	[38]

NOTE: GPR: G protein-coupled receptor; HDACs: histone deacetylases; RCTs: randomized controlled trials; TMAO: trimethylamine *N*-oxide; SCFAs: short-chain fatty acids; PAGln: phenylacetylglutamine; AMPK: AMP-activated protein kinase; FXR: farnesoid X receptor; TGR5: Takeda G protein-coupled receptor 5; AhR: aryl hydrocarbon receptor; SKN-1: Skinhead-1; ATFS-1: Activating Transcription Factor associated with Stress 1; *C. elegans: Caenorhabditis elegans.*

Table 3. Microbiota-targeted interventional and translational evidence relevant to aging

Study/Evidence Type	Intervention	Population/Age Range	Comparator	Duration/Status	Microbiome Endpoints	Clinical, Functional, and Safety Endpoints	Interpretation/PMID
PROMOTe Trial/RCT	Inulin + FOS prebiotic	Older twins; 36 pairs, ⩾ 60 years	Placebo	12 weeks/completed	*Bifidobacterium* abundance and microbiome composition	Cognition and muscle function; tolerability monitored	Improved cognition and increased *Bifidobacterium*; no significant muscle-function benefit[26]
Yang *et al*. 2024/RCT	Inulin + FOS prebiotic	Community-dwelling older adults; *N* = 200	Placebo	6 months/completed	Microbiome composition and metabolic function	Frailty status, walking speed, grip strength, inflammatory/nutritional markers	Improved frailty-related outcomes with microbiome changes[27]
Wastyk *et al*. 2021/Adult Dietary RCT	Fermented-food diet or high-fiber diet	Healthy adults; *N* = 36, not older-adult-specific	Parallel diet arms	17 weeks/completed	Microbial diversity and fiber-response patterns	Inflammatory markers; safety not aging-specific	Mechanistic diet-microbiome evidence, not an older-adult trial[39]
Li *et al*. 2025/Controlled Adult Diet Trial	Non-industrialized-type diet	Healthy adults; *N* = 30, not older-adult-specific	Controlled feeding comparator	3 weeks/completed	Microbiome composition and microbiota-derived metabolites	Cardiometabolic markers; safety not aging-specific	Translational diet evidence relevant to microbiome restoration, not geriatric RCT evidence[40]
ARMOR Study/RCT Protocol	FMT from young physically active donors	Older adults; target *N* = 80	Placebo/control product	6 months/protocol, results pending	Engraftment and microbiome composition	Physical function, frailty, feasibility, safety	Protocol only; no efficacy outcomes available[41]
Zhuang *et al*. 2025/Systematic Review and Meta-Analysis	Probiotics, prebiotics, synbiotics	Older-adult RCTs pooled	Placebo or usual-care comparators	4-24 weeks across trials	Beneficial taxa and community composition	Inflammation and clinical endpoints variably reported; safety heterogeneous	Synthesis of heterogeneous RCT evidence, not a single RCT[42]

NOTE: PROMOTe: PROtein and Muscle in Older Twins; FOS: fructooligosaccharide; ARMOR: Aging Resilience Through Microbiota Optimization and Regulation; FMT: fecal microbiota transplant.

2. Age-Associated Changes in Gut Microbiota Composition

2.1 The Microbial Trajectory across the Lifespan

The gut microbiota has a dynamic course during the whole life, until advanced age. The type of delivery, breastfeeding, diet, and antibiotic exposure define microbial colonization in the first years of life[43,44]. A more developed microbial population with greater diversity and a higher level of functional redundancy typically develops by about the age of three. In adult life, the core microbiome is relatively constant, but it can respond to diet, drugs, infection and lifestyle. The shift into advanced age, which in many human studies is specified as 60–65 years and over, is linked to the change of the microbial community structure that depend on the context, not to a uniform trajectory (**Figure 1A**).

2.2 Microbial Signatures of Older Adults

Several articles have reported that elderly people have less α-diversity than young adults[10]. Nevertheless, this trend does not apply to all; in exceptional cases, some reports of extremely healthy centenarians demonstrate preserved or even enhanced diversity[11,13], which implies that a high level of microbial diversity is not just one of the signatures of health, but can be actively used against pathological aging. Ecological support offered by certain functional microbial communities has to be met to activate such an endogenous driving force, but due to physiological aging, the keystone beneficial bacterial taxa that form this protective system decrease in number gradually and systematically (**Figure 1B**). The number of SCFA-producing bacteria, especially *Faecalibacterium prausnitzii* (*F. prausnitzii*), *Roseburia* spp., and *Eubacterium* spp., decreases steadily with age[10]. Another mucin-degrading bacterium associated with metabolic health and intestinal barrier integrity, *Akkermansia muciniphila* (*A. muciniphila*), is also found to be less abundant in older adults, especially in those who are frail[45]. Furthermore, Aging is related to a higher presence of facultative anaerobes, *Escherichia coli* (*E. coli*) and other *Enterobacteriaceae*, as well as a shift towards *Bacteroidetes*, at the expense of *Firmicutes*[46]. These changes are more apparent among institutionalized older adults than community-dwelling counterparts[15]. On the one hand, institutionalization negatively selects the gut microbiota by applying uniform low-fiber diets, aggressive drug treatments, restricted space, and increased frailty, which forces it into a pathological pathway of low diversity, high pro-inflammatory bacteria abundance, and lack of beneficial bacteria. On the other hand, in a community setting, people are able to keep a wider range of diets, fewer medical treatments and more social contact, which permits the microbiota to preserve more of the characteristics of healthy aging. It also explains why, in the context of understanding the microbiota of the elderly, one should not be preoccupied only with the concept of "age", but also with the concept of "where" and "how" one lives.

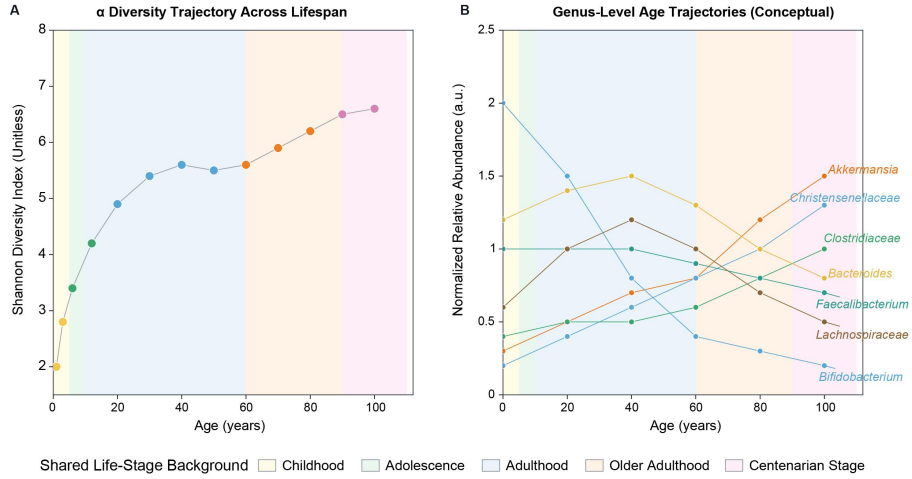


Figure 1. Age-associated trajectories of gut microbiota diversity and representative bacterial taxa across the human lifespan. (A) Figure 1A is a conceptual, non-quantitative schematic of gut microbial α-diversity dynamics across the lifespan, synthesized primarily from cross-sectional lifespan and longevity cohorts (Odamaki *et al*. 2016[10]; Kong *et al*. 2016[11]) rather than derived from a single raw dataset; (B) The taxon-level trajectories in Figure 1B were synthesized from published human cohort studies (Odamaki *et al*. 2016[10]; Kong *et al*. 2016[11]) reporting age-associated, frailty-associated, institutionalization-associated, and longevity-associated changes in representative taxa, including SCFA-producing bacteria, *Enterobacteriaceae*, *Akkermansia*, *Bifidobacterium*, *Christensenellaceae*, and *Clostridium* clusters IV/XIVa. Copyright: This figure was created by the authors using Python 3.12.13 and ReportLab 4.4.9. No third-party material was reproduced.

2.3 Centenarian Microbiome and Exceptional Longevity

The analysis of centenarians in Bama County, Guangxi, China, showed that *Roseburia* and *Escherichia* were found much more frequently, whereas *Akkermansia*, *Lactobacillus*, *Faecalibacterium*, *Parabacteroides*, *Butyricimonas* and *Coprococcus* were found much less frequently at the genus level than in individuals below 100 years of age[14]. Operational taxonomic units (OTUs) defined by age in this group were classified as *Ruminococcaceae*, *Clostridiaceae* and *Lachnospiraceae*, where the first two were higher in centenarians, implying that particular butyrate-producing lineages might be selectively conserved in the most extreme aging. Likewise, an investigation of a Chinese longevity population, together with cross-cohort analysis, demonstrated higher abundance of *Christensenellaceae*, *Akkermansia* and butyrate-producing *Clostridium* XIVa and *Clostridium* IV[11]. In a study of Italian half-supercentenarians (aged 105-109), Biagi *et al.*[12] reported a unique microbiota composed of health-related taxa such as *Akkermansia*, *Bifidobacterium* and *Christensenellaceae*, as well as a significant decrease in *Faecalibacterium* and other butyrate producers. These results supplement the results of Chinese centenarian groups in various geographic and nutritional environments. Such cross-population tendencies refute the idea that all age-related changes in microbiota are harmful and bring up the idea of the so-called healthy age-associated microbial configuration. Nevertheless, it is important to point out that centenarian microbiome research is by its nature vulnerable to survivorship bias. Those people who live to extremely advanced ages might have genetically robust microbiota arrangements to begin with. It is hard to separate life-long determinants of longevity from actual age-related adaptations. Moreover, causal inference is also constrained by the limited sample size that is common in centenarian cohorts and the cross-sectional designs of studies. DeJong *et al.*[47] have rightly warned that isolating cause and effect in the connection between gut dysbiosis and unhealthy aging constitutes an underlying issue. The interpretation of the observed microbial changes in elderly individuals as adaptive reactions, passive effects of physiological deterioration, or active causes of aging pathology probably depends on the context, host genetics, and environment. Representative human studies spanning lifespan, healthy aging, centenarian longevity, and frailty are summarized in **Table 1**.

3. Host-Driven Remodeling of the Gut Microbiota during Aging

The majority of accessible sources have focused on what role the gut microbiota plays in the process of host aging, but the opposite course, i.e., how the aging of the host organism restructures the microbial community, is also significant and rarely discussed. Immunosenescence alters the selective pressure of the mucosal immune system: decreased naive T cell production, decreased secretory IgA production and altered antigen-presenting cell function can upset the balance between tolerance and microbial containment[48,49]. The decline in mucosal immunity might allow the growth of taxa that would otherwise be limited, as has been observed with the age-related growth in *Enterobacteriaceae* and other facultative anaerobes in several cohorts[10,50,51]. Other physiological changes in the aging gastrointestinal tract, such as hypochlorhydria, slowed transit time, and changed mucus secretion, add more environmental filters. Such conditions might benefit oral-associated taxa like *Streptococcus*, *Veillonella*, and *Rothia*, facultative anaerobes like *Enterococcus* and *Enterobacteriaceae*, and mucus-adapted taxa like *Akkermansia*, *Bacteroides*, and mucin-degrading *Ruminococcus*; conversely, obligate anaerobic butyrate producers such as *Faecalibacterium*, *Roseburia*, *Eubacterium* rectale, and *Coprococcus* may be disadvantaged[52-54]. Medication exposure additionally confounds interpretation. Proton pump inhibitor medications raise gastric pH levels and have been associated with decreased microbial diversity and an increase in oral or higher gastrointestinal taxa in stool[7,52,53], whereas metformin can increase *A. muciniphila* and SCFA-producing bacteria, thereby confounding age-related signatures in metabolically unhealthy individuals. Microbial ecology may also interact with host genetics,

including longevity-related pathways such as apolipoprotein E (APOE) and forkhead box O3A (FOXO3A), although this field is not well-resolved enough to infer causality.

The reverse axis has not been considered as an independent caveat in the revised manuscript. Rather, every subsequent mechanistic and disease part is read as a feedback loop whereby host aging remolds microbial niches, microbial functions change host pathways, and disease or treatment conditions also change the gut environment. This structure also organizes the evidence by level: there are cohort studies which define population-associated signatures, experimental models which test microbe-to-host mechanisms, and intervention studies which determine if manipulation of the microbial ecosystem can enhance clinically significant aging phenotypes.

4. Microbial Functions and Metabolites as Intermediate Layer

4.1 Microbial Metabolites as a Central Functional Layer

Microbial metabolites provide the functional bridge between compositional shifts and host aging phenotypes (Table 2). Rather than treating taxa, organ axes, organelles, and cellular phenotypes as equivalent mechanisms, this review organizes the pathway from microbial community change to microbial metabolic output, then to cellular targets and systemic phenotypes. This framework helps reconcile apparently opposing effects: for example, SCFAs often support epithelial and immune homeostasis, yet in specific AD models they can also modulate microglia in ways that promote amyloid-β (Aβ) plaque deposition.

4.2 Short-Chain Fatty Acids and Intestinal Barrier Integrity

SCFAs, specifically acetate, propionate, and butyrate, are microbial metabolites produced during anaerobic fermentation of dietary fiber, host-derived mucins and certain amino acids or organic acids by commensal gut bacteria. They act as energy substrates for colonocytes, metabolic regulators, and signaling molecules by binding to G protein-coupled receptors (GPR) such as GPR41, GPR43, and GPR109A[16]. In the elderly, decreased fiber consumption along with a decrease in the SCFA-producing bacteria may decrease the availability of SCFA in the colon. Butyrate maintains the integrity of the intestinal barrier through induction of tight-junction formation, energy metabolism of epithelial cells, mucus balance and anti-inflammatory signaling. Microbial products like lipopolysaccharide (LPS) have been shown to translocate into the circulation when barrier function is compromised and cause systemic low-grade inflammation.

5. Mechanistic Pathways Linking the Gut Microbiota to Host Aging

5.1 The Gut Microbiota-Immunity-Inflammaging Axis

Chronic low-grade inflammation is one of the most repeatable immunological signs of aging[55,56]. This condition is also marked by continual, slight elevations in pro-inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and systemic factors such as C-reactive protein (CRP). At the same time, immunosenescence consists of lower naive T cell output, senescent-like T cells, new macrophage polarization, glial activation, and poor vaccine response[48,49,57]. In this setting, the gut microbiota has the potential to influence host immune homeostasis through the promotion of intestinal epithelial barrier integrity, mucosal immune balance, mucus-layer maintenance, SCFA synthesis and innate and adaptive immune-cell activity (Figure 2)[17,58,59]. The transfer of microbiota demonstrates that the aged donor microbiota may transfer inflammatory properties to young germ-free mice, such as alterations in the central nervous system, retina, and intestinal barrier[60,61]. These studies indicate that aged microbial communities have a mechanistic role in inflammaging, with causal evidence in human still lacking.

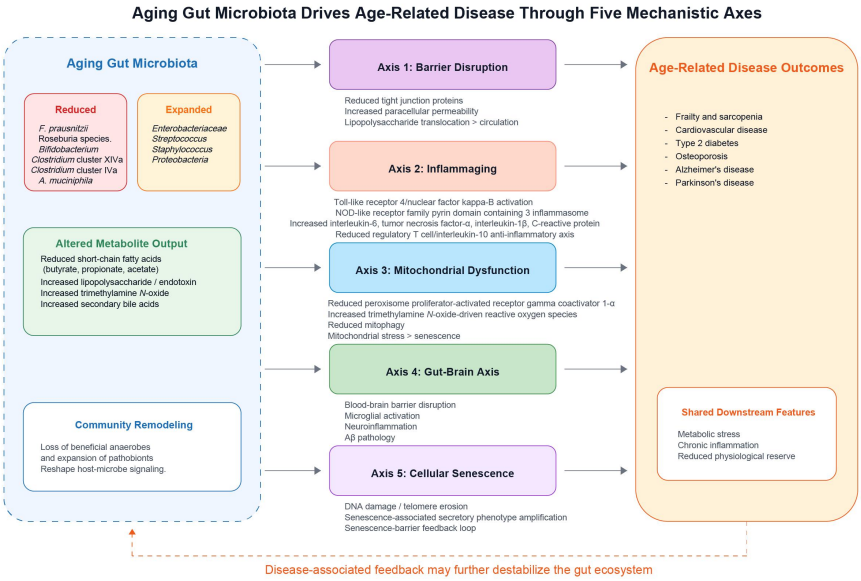


Figure 2. Mechanistic diagram of the microbiota-host aging axis. The diagram is an overview of the ways in which age-related changes in gut microbiota can be implicated in systemic aging and vulnerability to late-life disease. **NOTE:** *Clostridium* clusters XIVa and IV; spp.: several species in a genus; SCFAs: short-chain fatty acids; LPS: lipopolysaccharide; TMAO: trimethylamine *N*-oxide; TLR4: Toll-like receptor 4; NF-κB: nuclear factor kappa B; NLRP3: NOD-like receptor family pyrin domain-containing 3; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; CRP: C-reactive protein; Treg: regulatory T cell; IL-10: interleukin-10; ROS: reactive oxygen species; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-α; SASP: senescence-associated secretory phenotype; BBB: blood-brain barrier. Copyright: This figure was created by the authors using Python 3.12.13 and ReportLab 4.4.9. No third-party material was reproduced.

The loss of beneficial commensal bacteria with age may compromise an anti-inflammatory system that involves microbial butyrate. However, at the cellular level, butyrate induces the differentiation of colonic Forkhead box protein P3 (Foxp3)$^+$ regulatory T cells (Tregs). But this is achieved by the suppression of histone deacetylases (HDACs) and the upregulation of histone H3 acetylation on the Foxp3 locus[16,18]. Indigenous *Clostridium* clusters IV and XIVa, dominant butyrate-producing members of the *Firmicutes*, enhance Foxp3$^+$ Treg accumulation in the mouse colon. They are also involved in the production of Tregs that produce interleukin-10 (IL-10)[19]. The same effect has also been observed with microbiota-derived butyrate generated by the microbiota, which can act directly on Treg differentiation in the colon[18]. Some other immunomodulatory commensals play a role in this regulatory network. *F. prausnitzii* is capable of stimulating IL-10 production by human CD14$^+$ monocytes and changing cellular energy metabolism without eliciting a significant pro-inflammatory effect[20]. Secreted metabolites of the same species also prevent the activation of nuclear factor kappa B (NF-κB) by IL-1β and the production of interleukin-8 (IL-8)[21]. Butyrate-related community comprising *Clostridium* clusters IV and XIVa, *Roseburia*, *Eubacterium*, and *Bifidobacterium* mediated cross-feeding networks play a role in maintaining the integrity of the epithelial barrier, mucosal immunity as well as the systemic immune response via SCFA-dependent mechanisms[22]. When taken together, these results confirm the perspective which states that the butyrate-producing commensals are able to contribute towards maintaining mucosal homeostasis by both Treg-dependent and direct immunomodulatory mechanisms. Such regulatory networks can potentially be compromised with aging and inflammation. The loss of taxa like *Faecalibacterium*, *Roseburia*, and *Clostridium* clusters IV/XIVa could eliminate important protective signals. It is possible that a homeostatic circuit will transition to an inflammatory niche where facultative anaerobes and pathobionts can grow.

Recent animal research has demonstrated the proliferation of *Enterobacteriaceae* in aged *Caenorhabditis elegans* (*C. elegans*). Other gut microbiota members inhibit its spread and their pathogenic effects, indicating that the disruption of the ecosystem could permit the excessive growth of pathogens during aging[62]. Because the *Enterobacteriaceae* are Gram-negative bacteria, they have immunostimulatory molecules including LPS. If the integrity of the intestinal barrier is compromised, LPS-related signals can access the immune recognition pathways in the host and cause inflammatory reactions mediated by Toll-like receptor (TLR4)-NF-κB signaling. Kim *et al.*[63] found that the fecal and plasma LPS concentrations increased with age in mice[64]. They were also associated with activation of colonic NF-κB and upregulation of the expression of the inflammatory aging-related markers, namely p16 and SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1 (SAMHD1). It was also observed that intestinal contents and mucosal samples of old mice had more potent TLR4-activating ability. The transfer of aged microbiota to young germ-free mice enhanced the expression of IL-6, TNF and TLR4 in the colon. It was also associated with an increase in circulating LBP. Such results suggest that age enhances the immunogenic profile of the gut microbiota, and this is associated with a greater level of host inflammation.

These findings, taken together, suggest that microbiota-related inflammation cannot be explained by a single bacterial taxon. Instead, it can be viewed as an ecological dysbiosis that would include the loss of protective commensals, elevation in the levels of pro-inflammatory or immunogenic taxa, and changes in the metabolism of microbes[64]. Together, age-associated changes in the gut microbiota can cause weakening of the SCFA-Treg-IL-10 anti-inflammatory network and strengthening of the LPS-TLR4-NF-κB pro-inflammatory network. The alterations might enhance systemic immune activation through the disruption of the intestinal barrier and the rise in microbial-product translocation[65]. The gut microbiota ought thus not only to be viewed as a passive biomarker of immunosenescence but also as a modifiable factor in inflammaging.

5.2 The Aging Gut-Brain Axis in Neuroinflammation and Neurodegeneration

The gut-brain axis is the interconnection between the gut and brain via neural, neuroendocrine, immune, and circulatory routes. Gut dysbiosis in the elderly changes the signals of the microbiota (**Figure 2**). It also decreases the anti-inflammatory factors of SCFAs and tryptophan metabolites. It also raises the levels of pro-inflammatory factors, including lipopolysaccharides and secondary bile acids. These alterations can induce neuroinflammation, neurodegeneration and brain aging by disrupting the integrity of the intestinal barrier and blood-brain barrier, inducing peripheral inflammation, changing the vagal signal, and triggering microglia[36,37]. Gut dysbiosis may be related to brain aging and neurodegeneration through chronic low-grade inflammation. Animal studies of Alzheimer's disease show that dysbiosis of the gut has been linked to reduced expression of intestinal tight junction and adherens junction proteins. It is also correlated with the induction of the intestinal nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome and IL-1β signaling and the activation of microglia and astrocytes in the hippocampus. These results suggest a potential microbiota-intestinal barrier-inflammasome-brain axis[66]. Peripheral inflammatory signals may also compromise the integrity of the blood-brain barrier and change the central immune microenvironment. The process leads to microglial reactivity, neuroinflammation, and oxidative stress[67].

The SCFAs are critical mediators of microbiota-induced metabolic signaling across the gut-brain axis. Their role in maintaining the intestinal epithelial barrier and blood-brain barrier homeostasis is mediated by G-protein-coupled receptor signaling and histone deacetylase-dependent processes, and they can influence the activity of microglia[68]. Nevertheless, their protective effects are not uniform in AD models but are context-specific. Colombo *et al.*[69] demonstrated that SCFAs produced by the microbiota regulate microglia and can cause an increase in Aβ plaque formation in an amyloid mouse model, suggesting that SCFA signaling might have specific implications in relation to the stage of the disease or model used. Hence, any results concerning SCFAs in neurodegeneration need to be taken into in the context of the model, time point, disease stage, and inflammatory setting.

In contrast, people with Alzheimer's disease have an altered composition of gut microbiota. These changes have been linked to biomarkers of Aβ and tau pathology[70]. Mechanism studies indicate that in the case of intestinal inflammation, it can trigger C/EBPβ/δ-secretase signaling and stimulate the development and gut-to-brain spread of Aβ and tau fibrils[71]. Alzheimer-related microbiota might

also cause Aβ deposition and cognitive dysfunction by triggering polyunsaturated fatty acids (PUFA)-dependent neuroinflammation, the activation of microglia by *Bacteroides fragilis* and lipid metabolites, or by failing to clear Aβ by the microglia[72-74]. Microbiota of patients with Alzheimer's disease can lead to cognitive deficits and disruption of hippocampal neurogenesis in recipient animals. It is implied that the gut-brain axis could be involved in neurodegeneration due to microbial changes[75]. The evidence suggests that the microbiota of the gut plays a role in age-related deterioration of brain function by a sequential host-microbe interaction. The first step is dysbiosis, which causes changes in microbial metabolite profiles. Dysfunction of the intestinal barrier subsequently leads to systemic immune activation and neuroinflammation. These occurrences lead to the build-up of misfolded proteins, particularly Aβ and tau, and accelerate cognitive impairment.

5.3 Gut Microbiota Mitochondria Crosstalk in Aging

Mitochondrial dysfunction is an essential cellular characteristic of aging and age-related metabolic disorders[76]. Gut microbiota can influence mitochondrial homeostasis in the host through microbial metabolites and inflammatory signals. Intestinal microbial composition and metabolic output vary with aging (**Figure 2**). These alterations change microbiota-produced small molecules; they may influence mitochondrial oxidative phosphorylation, redox homeostasis, mitochondrial biogenesis and mitochondrial quality control.

Butyrate is an important microbiota-derived regulator of mitochondrial metabolism. It may increase activation of AMP-activated protein kinase (AMPK), upregulate peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) and facilitate oxidative metabolism in colonocytes and other metabolically active tissues. Age-related decline in butyrate-producing taxa could also be a contributing factor to poor mitochondrial resilience. Other metabolites produced by microbes act differently. A *C. elegans* model demonstrated that 3-phenyllactic acid improved mitochondrial performance and stress resistance via SKN-1/ATFS-1 signaling[38]. Phenylacetylglutamine (PAGln), a microbiota-derived aromatic amino-acid metabolite, increased the rate of cellular senescence in the host by inducing mitochondrial dysfunction and DNA damage through adrenoreceptor (ADR)-AMPK[34]. Gut microbial metabolism and mitochondrial stress are linked by TMAO: the gut microbes convert choline, phosphatidylcholine, and L-carnitine found in food into trimethylamine, which is then oxidized by host hepatic Flavin-containing monooxygenase 3 (FMO3). According to experimental evidence, TMAO induces the formation of mitochondrial reactive oxygen species, inhibits oxidative phosphorylation and causes either mitochondrial structural injury or remodeling induced by fission[28-31]. Since TMAO levels are related to the risk of cardiovascular and renal disease in adults, there is the possibility of this pathway linking gut dysbiosis, cardiometabolic aging, and organ-level mitochondrial dysfunction.

The existing studies on microbiota-mitochondria interactions in aging are mostly based on model organisms and *in vitro* systems. *C. elegans* and cell culture-based models can explain mechanisms, but these have obvious constraints for human aging studies. *C. elegans* does not possess an adaptive immune system and its gut structure is dissimilar. *In vitro* systems do not represent host-microbial and metabolic interactions between organs *in vivo*. More research should be done in mammalian systems and human participants who have paired metagenomic, metabolomic and mitochondrial functional outputs. The interaction of gut microbiota and mitochondria could be associated with changes in gut microbes, dysfunction of metabolic homeostasis and aging.

5.4 Gut Microbiota Imbalance and Cellular Senescence

Cellular senescence is a stable cell-cycle arrest with a senescence-related secretory phenotype (SASP). Despite the fact that cellular senescence is an old-established hallmark of aging, it has been studied in connection with the gut microbiota only relatively recently. A microbial product might trigger senescence-like pathways in the host tissues during inflammation or genotoxicity and senescent epithelial and immune cells have the ability to remodel the intestinal niche in such a way that impacts microbial attachment and access to nutrients (**Figure 2**). Older guts are subject to greater levels of LPS and other pathogen-associated molecular patterns that can initiate TLR4-NF-κB signaling and maintain SASP-like inflammatory programs. Premature senescence and SASP features can be triggered by bacterial genotoxins like colibactin in colon epithelium or tumour cells[77-79]. Vice versa, senescent cells can change the mucus configuration, epithelial glycosylation and matrix reconstruction by SASP mediators. These modifications may benefit taxa that are adapted to mucus use at the expense of unadapted competitors because gut bacteria utilize host-derived glycans and mucus as sources of nutrition and attachment[80,81]. The microbiota-senescence axis is therefore better seen as an ecosystem cycle rather than a straightforward cause-effect interaction

6. Age-Related Diseases and Functional Decline

6.1 Cardiometabolic Diseases

Cardiometabolic diseases are frequent age-related diseases where gut microbiota can affect disease risk and progression. Such disorders include atherosclerotic cardiovascular disease, hypertension, heart failure, type 2 diabetes (T2D), chronic kidney disease, and metabolic dysfunction-related steatotic liver disease. It is associated with gut microbiota-derived metabolites, intestinal barrier function and inflammaging. Alterations in gut microbes in trimethylamine *N*-oxide, bile acid, and aromatic amino acid metabolism could cause atherosclerosis, heart failure, and other significant adverse cardiovascular outcomes. Such pathways have been linked to lipid metabolism, platelet activation, vascular inflammation and myocardial metabolism[35,32,82]. Changes in microbial population have also been observed in patients with T2D. A systemic review conducted recently has shown positive correlations of *Escherichia* and *Shigella* with T2D, and negative correlations of *Akkermansia*, *Bifidobacterium*, *Roseburia* and *Faecalibacterium* with T2D. These results indicate that gut dysbiosis might contribute to obesity, T2D, atherosclerosis, and heart failure by decreasing short-chain fatty acid production, barrier dysfunction, inflammation induction, and aberrant microbial metabolite profiles[83] (**Figure 3**).

The relationship between the gut microbiota and cardiometabolic aging can be divided into three main axes. Firstly, the loss of SCFA-mediated regulation of metabolism and barrier support could lead to the development of insulin resistance and metabolic endotoxemia. Secondly, TMAO is associated with atherogenesis, platelet hyperreactivity and mitochondrial stress. Thirdly, LPS-TLR4 signaling might cause inflammation in endothelial cells and NLRP3 inflammasome activation. Much of the current human evidence is observational and is affected by diet, medications, comorbidities, age, and geography. Therefore, it is important to consider the gut microbiota as a disease modifier, risk indicator, and potential therapeutic target of cardiometabolic disease rather than as an individual causal factor.

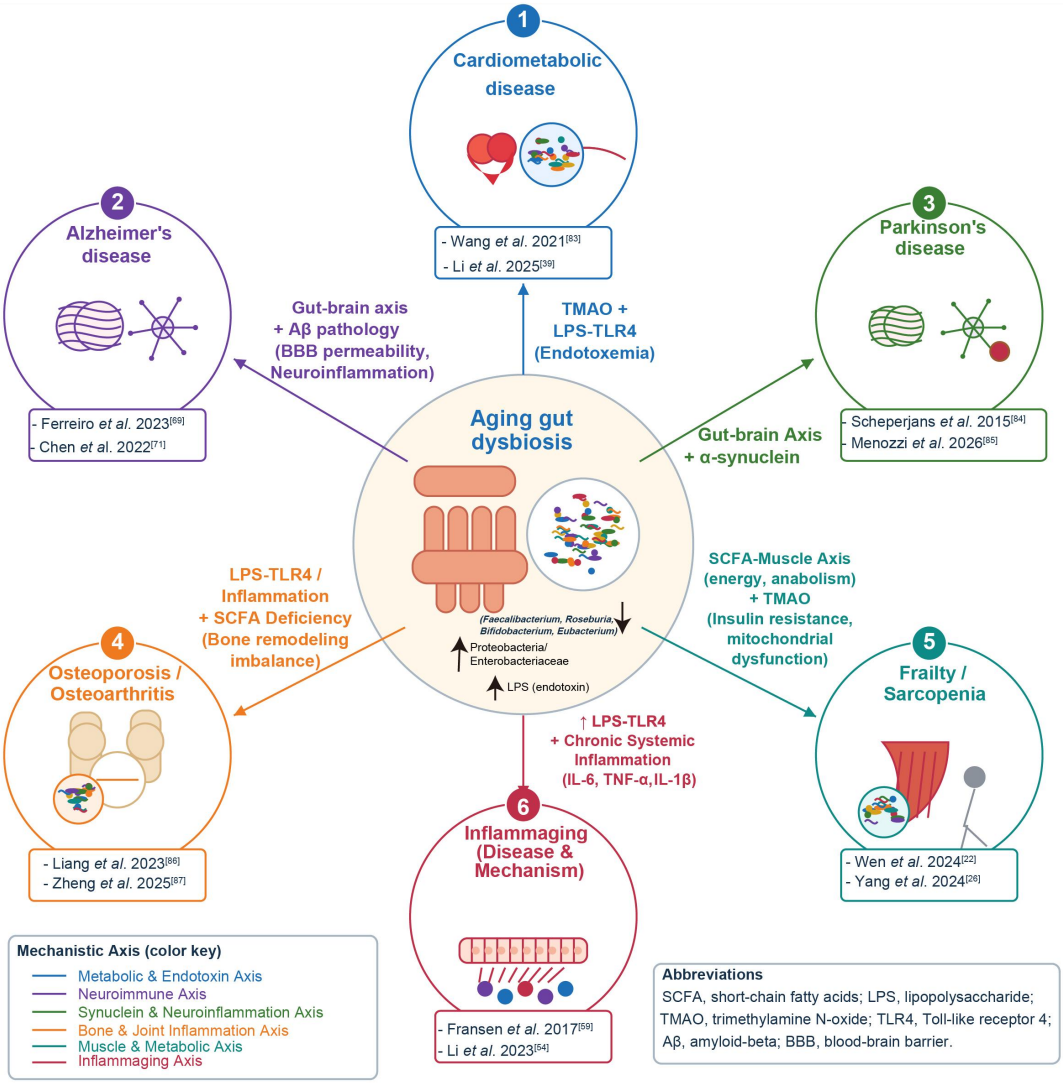


Figure 3. Gut microbiota in age-related diseases-multi-axis disease connections. Aging-associated gut dysbiosis is characterized by reduced SCFA-producing bacteria, increased Proteobacteria/Enterobacteriaceae, decreased microbial diversity and elevated LPS. These changes may promote cardiometabolic disease, Alzheimer's disease, Parkinson's disease, osteoporosis/osteoarthritis, frailty/sarcopenia and inflammaging through multiple mechanistic axes, including endotoxemia, gut-brain signaling, neuroinflammation, bone-joint inflammation, SCFA deficiency, TMAO accumulation and systemic LPS-TLR4 activation[23,27,40,55,60,70,72,84-88]. Module 6. Each colored sphere represents a different inflammatory factor, as indicated in the figure legend: Purple, IL-6; Red, TNF-α; Blue, IL-1β. Copyright: The figure was created by the authors using Python 3.12.13 and ReportLab 4.4.9. No third-party material was reproduced.

6.2 Neurodegenerative Diseases

Among the neurodegenerative diseases in which the changes in gut microbiota have been explored most extensively in elderly people are AD and PD (Figure 3). To minimize duplication with Section 5.2, this subsection will be devoted to disease-related microbial signatures and interpretation. Patients with AD usually have an increase in pro-inflammatory or opportunistic taxa, such as *Enterobacteriaceae* and *Escherichia*/*Shigella*, and a decrease in SCFA-producing or anti-inflammatory taxa, including *Faecalibacterium*, *Roseburia*, *Eubacterium rectale*, *Coprococcus*, and *Bifidobacterium*[89,90]. Mechanistic experiments indicate that AD-related microbiota may affect Aβ deposition, microglial activation, and neuroinflammation as well as hippocampal neurogenesis by means of several pathways, such as PUFA-based neuroinflammation and metabolites of lipid metabolism involving *Bacteroides fragilis*, and failure of microglial clearance of Aβ[72-75].

In PD, pooled studies and metagenomics studies have found increased levels of *Akkermansia*, *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and opportunistic *Proteobacteria* along with decreased levels of Prevotella and SCFA-producing taxa such as *Faecalibacterium*, *Roseburia*, *Blautia*, and *Coprococcus*[85,91,92]. The changes are associated with mucus barrier homeostasis, LPS-driven inflammation, α-synuclein pathways, neuroactive metabolism and levodopa metabolism. More recent findings in PD patients and asymptomatic *glucosylceramidase beta 1* (*GBA1*) variant carriers indicate that microbiome profiles might be used to determine early risks, but their predictive and causal utility needs longitudinal and intervention studies to confirm their utility[86].

6.3 Osteoarticular Diseases and Osteoporosis

Osteoarthritis (OA), osteoporosis, and certain immune-related osteoarticular diseases are of clinical significance in older adults and have attracted focus in the studies of the gut-joint and gut-

bone axes (**Figure 3**). The understanding of OA has shifted towards a holistic picture of the whole-joint disease including cartilage, synovium, subchondral bone, low-grade inflammation, and a metabolic imbalance. Gut dysbiosis can affect the joint microenvironment by compromising intestinal barrier integrity, microbial translocation, increased circulating LPS, and chronic low-grade inflammation leading to synovitis, cartilage matrix disintegration, subchondral bone reconstruction, and pain sensitization[93,94]. Rheumatoid arthritis (RA) is not a traditional age-related degenerative joint disease; it is mentioned in this context as an immune-mediated osteoarticular comparator since RA research offers mechanistic clues about microbiota-immune-joint interactions that are relevant to inflammatory joint pathologies. RA cohorts also tend to have increased levels of *Prevotella copri* and *Collinsella* and lower amounts of anti-inflammatory taxa[95,96]. Osteoporosis is more closely linked to musculoskeletal aging and is associated with changes in the gut-bone axis, such as the loss of beneficial taxa, opportunistic bacteria (*Klebsiella* and *Escherichia-Shigella*) in some cohorts, decreased SCFA production, changes in calcium absorption and immune-mediated bone resorption[87,88,97]. Amino-acid metabolism, *Bacteroides vulgatus*-valeric acid pathway, arginine metabolism, and TMAO are also implicated in bone remodeling and osteogenic differentiation in multi-omics and experimental findings[33,98,99]. In general, the microbiota ought to be considered as a disease-modifying and possibly targetable variable of musculoskeletal aging and not as a well-established cause of OA, RA, or osteoporosis.

6.4 Frailty and Sarcopenia as Functional Aging Phenotypes

Frailty and sarcopenia are two major geriatric syndromes that better express biological aging as opposed to chronological age (**Figure 3**). Frailty is defined as decreased physiological reserve and high susceptibility to stressors, and sarcopenia is defined as an ongoing, systematic decline in the amount, power, and function of skeletal muscle. Sarcopenia is not only a part of but also a cause of the frailty phenotype.

Epithelial and metabolic pathways, as well as immune system mechanisms and potentially direct myocellular effects, can be used to explain how SCFAs produced by the gut, especially butyrate and propionate, can affect muscle mass and function. Relevant SCFA-producing or cross-feeding taxa comprise *F. prausnitzii, Roseburia* spp., *Eubacterium rectale*, *Coprococcus* spp., *Blautia* spp., *Anaerostipes* spp., *Prevotella* spp. and *Bifidobacterium*. The disappearance of such populations in frail elderly people may decrease microbial fermentation, damage the integrity of the epithelial barrier, decrease their insulin sensitivity, and increase the levels of chronic low-grade inflammation, thus promoting the breakdown of muscle proteins and functional deterioration[23-25]. On the other hand, bacteria that generate trimethylamine, such as *Enterobacteriaceae* (*E. coli* and *Klebsiella* spp.) and certain members of the *Clostridiaceae* and *Desulfovibrionaceae* (choline TMA-lyase (*cutC*) or carnitine oxygenase/reductase (*cntA/B*)), can promote TMAO production by converting dietary choline and carnitine. TMAO-induced metabolic stress could indirectly induce skeletal muscle dysfunction through cardiometabolic, renal, inflammatory, and mitochondrial pathways[28-31,33]. Indole and p-cresol precursors are produced by proteolytic and amino-acid-fermenting bacteria, such as tryptophanase-positive *Enterobacteriaceae* and p-cresol-producing *Clostridia*, which are converted by the host to indoxyl sulfate and p-cresyl sulfate; these uremic toxins can accumulate with age-related renal decline and further inhibit muscle differentiation, mitochondrial biogenesis, and protein homeostasis. This overall effect of the gut microbiota on the aging of muscles might consequently represent an equilibrium between beneficial SCFA-producing groups and harmful TMAO-producing groups or uremic-toxin-generating metabolic circuits.

Cross-sectional research has linked frailty to specific microbial profiles, such as reduced levels of *F. prausnitzii*, *Roseburia* species, and other SCFA producers in frail older adults compared with robust older adults. Prebiotic supplementation was found to enhance cognitive function and boost *Bifidobacterium* levels in older people participating in the PROtein and Muscle in Older Twins (PROMOTe) trial[26]. Randomized controlled trials (RCTs) have also shown better results in outcomes related to frailty, such as walking speed and grip strength, after prebiotic intervention[27]. Strong evidence for interventions targeting the microbiota to prevent or reverse sarcopenia in older adults remains limited. RCTs should recruit more participants, follow them longer, and use functional endpoints.

7. Microbiome-Targeted Interventions and Therapeutic Opportunities

7.1 Dietary Intervention

The easiest and most scalable method of microbiome targeting is dietary modulation, which promotes healthy aging. In contrast to more specific interventions like probiotics and FMT, dietary intervention can constantly alter the substrates that are presented to the gut microbiota and the intestinal metabolic milieu and thus alter the microbial composition and functional pathways (**Figure 4**). High-fiber diets, high-polyphenol diets, and fermented food diets may encourage the production of SCFAs by microbes and polyphenol-derived metabolites with possible benefits for the integrity of the intestinal barrier, chronic low-grade inflammation, and cardiometabolic homeostasis. As per recent studies, it was found that there were particular gut microbial taxonomic and functional profiles associated with adherence to the Mediterranean diet and that this association could be partially explained by the role of gut microbiota composition as a mediator in its protective association with cardiometabolic risk. Greater microbial diversity has also been associated with higher carbohydrate quality, higher abundance of potentially beneficial taxa like *Faecalibacterium* and the *Christensenellaceae* R7 group, and better metabolic profiles. The microbial signatures related to the Mediterranean diet have been connected to lower rates of cognitive decline in older high-risk groups, which adds to the possibility that the diet-microbiota-metabolic/immune system plays a part in healthy aging[84,100,101]. Other randomized dietary intervention studies suggest that fermented foods may enhance gut microbial diversity and decrease inflammatory markers, whereas a microbiome-restorative diet based on non-industrialized eating habits may restore the microbial characteristics of industrialization, change the plasma metabolites produced by the microbiota, and optimize certain cardiometabolic phenotypes[39,40]. Taken together, these results indicate that dietary modulation is a feasible approach to remodeling the gut microbiome in healthy aging, yet long-term compliance, inter-individual microbiome variation, and the causality of effects on clinical outcomes of aging need additional research.

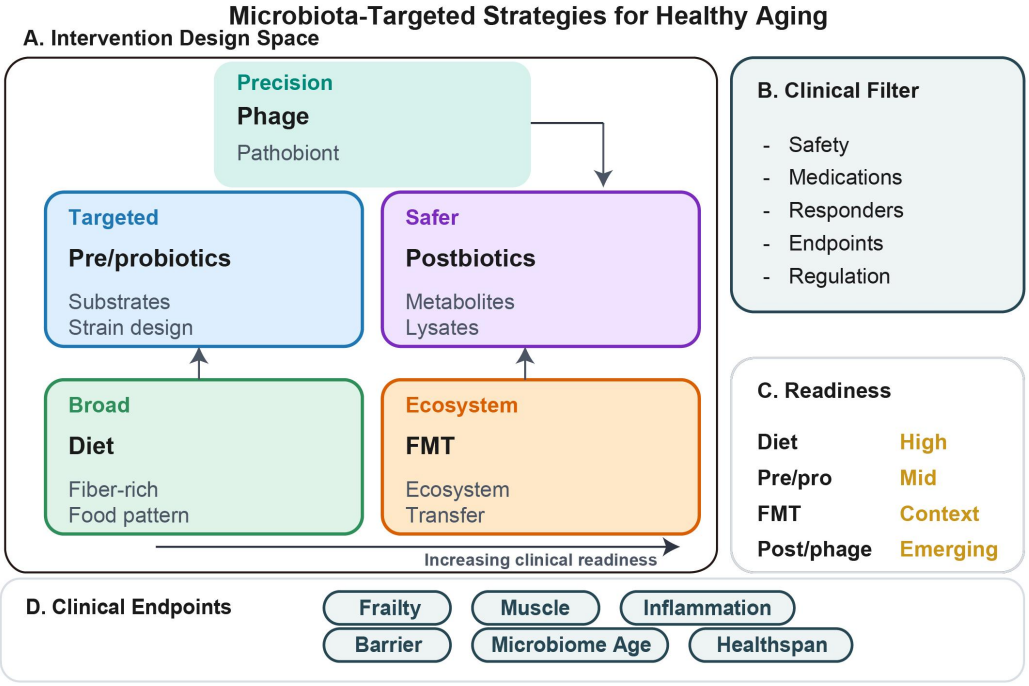


Figure 4. Translational framework for microbiota-targeted interventions in healthy aging. The diagram below displays the organization of microbiota-directed strategies along a continuum of increasing mechanistic specificity and clinical applicability. Broad-based methods (i.e., diet modulation) are characterized as the most readily implementable first-line options, whereas prebiotics/probiotics, FMT/SMC, postbiotics and phage-based methods will be viewed as more specific to distinct mechanisms or directed towards modulating the microbiome as a whole. Clinical development is established by assessability of safety, pharmacologic use; responder characteristics, functional outcomes, and regulatory viability; with the primary geroscience trial outcomes including frailty, muscle performance, inflammation, intestinal barrier function, microbiome age, and healthspan. (A) Intervention design space; (B) Clinical filter; (C) Readiness; (D) Clinical endpoints. **NOTE:** FMT: fecal microbiota transplant. Copyright: The figure was created by the authors using Python 3.12.13 and ReportLab 4.4.9. No third-party material was reproduced.

7.2 Probiotics, Prebiotics, and Synbiotics

These are promising, however, not fully tested methods of microbiota modulation in healthy aging: probiotics, prebiotics, and synbiotics. Prebiotic substances selectively promote the growth of beneficial commensals, especially *Bifidobacterium* and cross-feeding networks of SCFAs, which have an impact on microbial fermentation, metabolic homeostasis and immune regulation (**Figure 4**). Randomized studies in older adults have demonstrated that inulin-based and fructooligosaccharide-based prebiotics enhanced frailty-related outcomes like walking speed and grip strength in one community-based study[27], whereas the PROMOTe trial enhanced cognitive performance and raised the number of *Bifidobacterium* without a substantial improvement in muscle function[26]. There is a recent meta-analytic finding indicating the ability of probiotics, prebiotics, and synbiotics to enhance the beneficial taxa and alter inflammation or metabolite levels in the elderly, but this varies by formulation, dose, initial diet, host microbiota, and length of intervention[42]. Further long-term mechanistic studies with functional endpoints are required before they can be suggested as standardized geriatric interventions.

7.3 Fecal Microbiota Transplantation

The most extreme method of microbiome manipulation is FMT (**Figure 4**). Although FMT has shown impressive effectiveness in the treatment of recurrent *Clostridioides difficile* infection, which especially affects the elderly or institutionalized individuals, its use in the management of age-related conditions is still experimental[102]. The preclinical research on mice indicates that FMT using young donors is able to restore some characteristics of aging in old recipients, such as cognitive impairment, immune senescence, and metabolic dysfunction[61].

The safety concern regarding the application of FMT to older people presents unique safety concerns that cannot be adequately addressed by the existing evidence. Older individuals are commonly linked with relative or absolute immunosuppression owing to immunosenescence, other comorbidities, and other treatments that bring about immunosuppression; hence, they are prone to FMT-linked infections. In 2019, two immunocompromised patients developed donor-derived extended-spectrum beta-lactamase (ESBL)-producing *E. coli* bacteremia following FMT, with one death reported[103]. In 2020, the FDA also warned against severe cases of infection caused by enteropathogenic *E. coli* and Shiga toxin-producing *E. coli* following investigational FMT, including two fatalities after administration of a product sourced from a Shiga toxin-producing *Escherichia coli* (STEC)-related donor; the causality was not conclusively identified. They underline that FMT is not a no-risk treatment. Rigorous donor screening measures, such as not accepting those with potential transmissible diseases, metabolic disease vulnerability, or microbial fingerprints of frailty, must be adopted. The role of the age of the donor has emerged as a deciding factor: it has already been acknowledged that younger donors will provide a richer and more functional microbial inoculum, but the optimal donor age range in indications involving aging has not yet been established.

Evidence level and current limitations. FMT has been reported to be of preclinical to early clinical evidence status in aging-related

symptoms. The Aging Resilience Through Microbiota Optimization and Regulation (ARMOR) Study[41] is a randomized, double-blinded, placebo-controlled study of the use of young, physically active donor-derived FMTs to promote resilience in old age and is the first well-designed clinical plan in this area that will offer important information on feasibility, safety, and preliminary efficacy. Outside of Clostridioides difficile infection (CDI), there are no approved FMT protocols to treat any age-related illness. Safety data over time are basically non-existent, and questions regarding the possible transplantation of pro-aging microbial profiles, the sustainability of engraftment in the older intestine, and how often and through which pathway it should be administered have not been resolved yet. FMT as a strategy to achieve healthy aging is now an investigational approach that should only be used in carefully controlled clinical studies.

7.4 Emerging Strategies: Postbiotics, Metabolite Therapeutics, and Phage Therapy

Besides live microbial interventions, emerging non-live or precision methods also warrant independent attention. Postbiotics should be understood in the context of consensus usage that states they are preparations of inanimate microorganisms and/or their components that impart a health benefit; purified microbial metabolites, such as SCFA formulations, are more appropriately described as stand-alone microbiota-derived metabolite therapeutics than postbiotics[104-106]. Such a difference is significant to elderly, weak, or immunocompromised groups since non-live microbial products might preserve immunomodulatory or barrier-promoting bioactivity, without causing any of the hazards involved in taking viable microorganisms. Targeted colonic propionate delivery falls into this general category, but is a different strategy[107]. Phage therapy is a precise treatment used to reduce pathobionts, such as *E. coli* or *Klebsiella pneumoniae*, with lytic phages whilst sparing most commensal taxa; combinations of phages have demonstrated potential in concept as an effective mechanism to reduce disease-causing gut commensals in intestinal inflammation[108]. In the context of aging, both postbiotic/metabolite and phage-based approaches are still in the initial stages of development and need to be tested for safety, efficacy, and ecological stability at specific ages. **Table 3** highlights key microbiota-targeted randomized controlled trials in older adults.

8. Challenges and Future Directions

Several fundamental questions remain unresolved in the field of gut microbiota and aging research.

Causality and correlation. The majority of the human studies are still cross-sectional, which constrains the possibility of establishing if the changes in microbes can occur before the aging phenotype or are a consequence of host aging, or both. Temporal relationships will require longitudinal cohorts with repeated microbiome sampling starting in midlife and continuing until late life. Causal inference may be enhanced by Mendelian randomization and gnotobiotic or microbiota-transfer models, but each method makes assumptions and has limitations. To make causal claims with confidence, randomized interventions demonstrating that manipulation of microbiota provides sustained functional benefits in older people will be necessary.

The confounding factors. Proton pump inhibitors, metformin, antibiotics, and non-steroidal anti-inflammatory drugs are commonly used medications among the older population and they play an important role in affecting the gut microbiome. Much of the literature fails to adequately address these confounders. The implementation of comprehensive medication reconciliation during future studies, along with analysis of drug-microbiome interactions, should become an accepted practice. To isolate age-specific microbial signals, it would be necessary to create medication-adjusted microbiome indices to isolate age-specific microbial signals.

Taxonomic profiles may be applied in order to produce what is known as microbiome aging clocks[109], which is an innovative approach that enables measuring biological age with the help of a stool sample and the assessment of interventions to reverse microbiome aging. Since then, the field has advanced at a rapid pace, starting with the pioneering contribution of Galkin *et al*[109]. Cross-cohort gut microbiome datasets have been used to train deep-learning and multi-view machine-learning models that demonstrate that taxonomic and functional microbiome profiles can predict chronological age. Newer gut microbiome aging-clock studies also indicate that residual microbiome-predicted ages are related to health and frailty risk, whereas corresponding cohort and intervention studies show that age-dependent microbiome profiles predict survival and can be changed by diet interventions[109,110]. In 2026, Ticinesi *et al.*[111] performed a systematic review of the contributions of the gut microbiome to the aging process and frailty risk and mentioned the potential involvement of biomarkers associated with the microbiome in geriatric risk stratification but cautioned that metagenomics of a single-time-point stool may represent transient rather than steady aging signals.

Personalized interventions. Due to the significant inter-individual variability in the gut microbiota composition, especially in elderly individuals, stratified/personalized intervention depending on the microbiome might be necessary. Factors affecting the effectiveness of intervention include baseline composition of microbiota, diet, genetics, and frailty status. It has been demonstrated that responder and non-responder microbiota types may be applied to dietary fiber interventions with regard to SCFA production and may also be used for other microbiota-directed interventions in aging populations.

Non-bacterial members. Research on the gut virome, mycobiome, and archaeome in the context of aging has not been widely performed. These elements of the gut ecosystem may be related to bacterial communities and the physiology of the host in the context of aging. A bacteriophage-dominated gut virome has the ability to influence the bacterial community structure through predation and gene transfer across species. Early information suggests that the content of the virome varies with age and could possibly be a component of the dysbiotic pathway, but this has not yet been studied systematically in the older population.

9. Conclusion

The structure and role of gut microbiota frequently change over a lifetime, such as decreased SCFA-producing commensals, increased facultative anaerobes/pathobionts, changes in microbial metabolite production, and alterations in the diversity of the community. Nevertheless, such tendencies are diverse and vary based on health, frailty, residential setting, diet, medication use, location, and number of diseases. Dysbiosis is included in the broadened hallmarks-of-aging model; however, existing evidence in humans does not confirm its status as a separate cause of aging that is on par with chronic inflammation. Less boldly, I would suggest that the interaction

between gut microbial dysbiosis and inflammaging, immunosenescence, metabolic dysfunction, mitochondrial stress, and cellular senescence might form the basis of later-life paths.

The main conclusion of this review is twofold: aged host physiology that has the ability to change gut microbiota due to immunosenescence, changes in the conditions of the gastrointestinal tract, medications, and genetic history, and microbial metabolites and inflammatory signals can exert a feedback effect on host tissues. The given host-microbe feedback architecture could be helpful in classifying physiological aging, exceptional longevity, frailty, and age-related diseases.

SCFAs, TMAO, PAGln, bile acids, tryptophan derivatives and other microbial metabolites, as well as uremic microbial toxins, offer a mechanistic link between taxonomic remodeling and host cellular pathways. The potential of dietary manipulation, prebiotic supplements, specific probiotic strains and other well-controlled experimental methods like FMT, postbiotics, metabolite therapeutics and phage-based therapies has been shown, however, its application to aging needs to be balanced with the level of evidence and safety profile. Microbiome-derived markers can eventually be used as an add-on tool to risk stratify geriatrics, but it still requires prospective validation, technical standardization, reproducible microbiome-aging clocks, stratification of responders, and clinical utility demonstration before it can be routinely employed in geriatrics.

Author Contributions

Conceptualization, Chenyu Guo and Zengren Zhao; literature search and data curation, Chenyu Guo, Kejun Li and Zhixing Wang; writing-original draft preparation, Chenyu Guo and Kejun Li; writing-review and editing, Zhixing Wang and Zengren Zhao; supervision and funding acquisition, Chenyu Guo and Zengren Zhao. All authors have read and agreed to the published version of the manuscript.

Artificial Intelligence (AI) Statements

During the preparation of this manuscript, during the preparation of this manuscript, the authors used AI-assisted drafting in Codex to support the conceptual drafting of the Graphical Abstract and the main figures. The final Graphical Abstract and main figures were programmatically drawn as editable vector graphics by the authors using Python 3.12.13 and ReportLab 4.4.9. No third-party material was reproduced. After using these tools, the authors carefully reviewed, verified, and edited all generated or modified content and accept full responsibility for the integrity and accuracy of the manuscript.

Conflicts of Interest

The authors declare no competing financial interests.

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