

REVIEW

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Microbiome-based therapeutics towards healthier aging and longevity

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Abstract

The gut microbiome is our lifetime companion, regulating our health from birth throughout the lifespan. The gut microbiome composition changes continually with age, influencing both physiological and immunological development. Emerging evidence highlights the close association, and thus implication, of the microbiome with healthy disease-free aging and longevity. Accordingly, targeting the gut microbiome is emerging as a promising avenue to prevent, alleviate, and ameliorate aging-related disorders. Herein, we provide a prospective and inclusive framework of the close connection of the gut microbiome with human aging, while contemplating how this association is intertwined with age-related diseases. We delve into recently emerging and potential microbiome-based therapeutics that are projected to aid in alleviating myriad aging-related diseases, thereby enhancing the health and well-being of the aging population. Finally, we present a foundation and perspective underlining the prospects of microbiome-based therapeutics developed and tailored precisely for the elderly, with the overarching goal of promoting health and longevity.

Keywords Gut, Microbiota, Metagenomics, Dysbiosis, Geriatrics, Senescence, Inflammaging, Probiotics, Prebiotics, Postbiotics

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Background

Aging is a natural physiological process that includes the gradual decline and progressive senescence of basic physiological functions. As we age, senescence accelerates, leading to intracellular damage accumulation and increased predisposition to age-related disorders [1]. Emerging evidence, through comprehensive and large-scale metagenomic studies from around the world, has suggested close interaction of the gut microbiome with human aging and aging-associated health status [2–4]. The human gut microbiome, a densely populated and diverse microbial community, exists in symbiotic harmony with the host and within itself, continually adapting and realigning in response to the host's environment and lifestyle across the lifespan [5]. However, disruptions in the gut microbiome, driven by intrinsic or extrinsic elements, can disrupt microbial homeostasis, leading to a state of “dysbiosis,” which can induce or exacerbate the onset of different age-related diseases (ARDs) through multidirectional communication axes involving host intestinal, cardiometabolic, immune, and/or neurocognitive health [6]. Recent research demonstrates the potential of microbiome-targeting therapeutics to promote healthy aging by preventing/ameliorating ARDs [7–10]. Thus, a precise understanding of natural and environmentally induced microbiome alterations, including disease-specific taxa and their metabolic functions, is crucial for developing personalized therapies for older adults [4]. Aging-associated changes in the gut microbiome may serve as primary determinants of late-life health. In this context, novel and emergent strategies to optimize the microbiome for therapeutic purposes could extend healthspan and lifespan, while reducing global healthcare costs. To this end, we herein present a perspective on emerging research wherein we deliberate the topical concept of targeting the gut microbiome and dysbiosis as a potential therapeutic target for ARDs. Sequentially, we summarize and deliberate recent advances pertaining to the incipient potential of microbiome-based therapeutics to promote healthy aging and longevity (Fig. 1). Finally, we introduce and propose the term “biome-aging” to denote the concept of such aging-associated microbiome transformations during different stages of our lifespan. In introducing biome-aging, we emphasize how cumulative changes in the gut environment—from shifts in barrier integrity and nutrient absorption to the effects of polypharmacy—progressively remodel microbial communities. This dynamic favors a decrease in beneficial microbes, an upsurge in pathobionts, and heightened inflammatory responses at both the local and systemic levels. By defining biome-aging, we underscore the importance of preserving a balanced gut ecosystem in older adults and

open new possibilities for mitigating health risks tied to accelerated or pathological aging (Fig. 1).

The concept and mechanism of biome-aging

The distinction between gut dysbiosis as a hallmark feature versus a causative factor of unhealthy or accelerated aging and related ARDs is only beginning to be resolved. Systemic low-grade chronic inflammation—marked by elevated interleukin (IL)–1, IL-6, and tumor necrosis factor alpha (TNF α)—has emerged as a key driver of ARDs [11]. This condition, known as “inflammaging,” contributes to gut microbiome dysregulation via its tight interplay with the host immune system. This potential bidirectional communication between inflammaging and dysbiosis, in the context of biome-aging, can be influenced by specific external stimuli. For instance, factors including polypharmacy, physical inactivity, social isolation, hormonal changes due to gastrointestinal tract (GIT) deterioration, and malnutrition are all known to influence human aging as well as biome-aging. The overprescription of non-antibiotic medications has also been linked to severe changes in the GIT and decreased gut microbiome diversity in aging model studies [12]. Medications are known to induce changes in appetite, ability to absorb certain nutrients, and dry mouth, leading to decreased salivary enzyme production [13]. Together, polypharmacy and malnutrition reduce fiber intake and beneficial gut bacteria involved in pathogen defense, barrier integrity, and production of short-chain fatty acids (SCFAs), vitamins, mucin, and neurotransmitters [12]. These collective impacts trigger a hyper-inflammatory (or proinflammatory) state both locally and systemically. Furthermore, reduced fiber intake leads to dysregulated gut motility and colonic transit, characterized by symptoms such as constipation, bloating, diarrhea, and nausea [13]. Additionally, the degeneration of the myenteric plexus within the enteric nervous system (ENS) further impairs and exacerbates these disorders. Along with accelerated expression (upregulation) of cellular senescence markers in the colonic region of the myenteric plexus, the number of enteric neurons also begins to decline in the myenteric plexus of older adults [14]. Aging-related increases in gastric pH, often caused by chronic atrophic gastritis, lead to achlorhydria and hypochlorhydria as a result of reduced glandular function in the gastric mucosa [15]. Elevated gastric pH may also promote the overgrowth of *Helicobacter pylori* and other pathobionts [16]. With age, intestinal epithelial cell (IEC) function declines, and intestinal stem cells lose their self-renewal capacity, impairing tissue rejuvenation and healing. Eventually, the senescence of IECs, particularly enterocytes and goblet cells, results in diminished

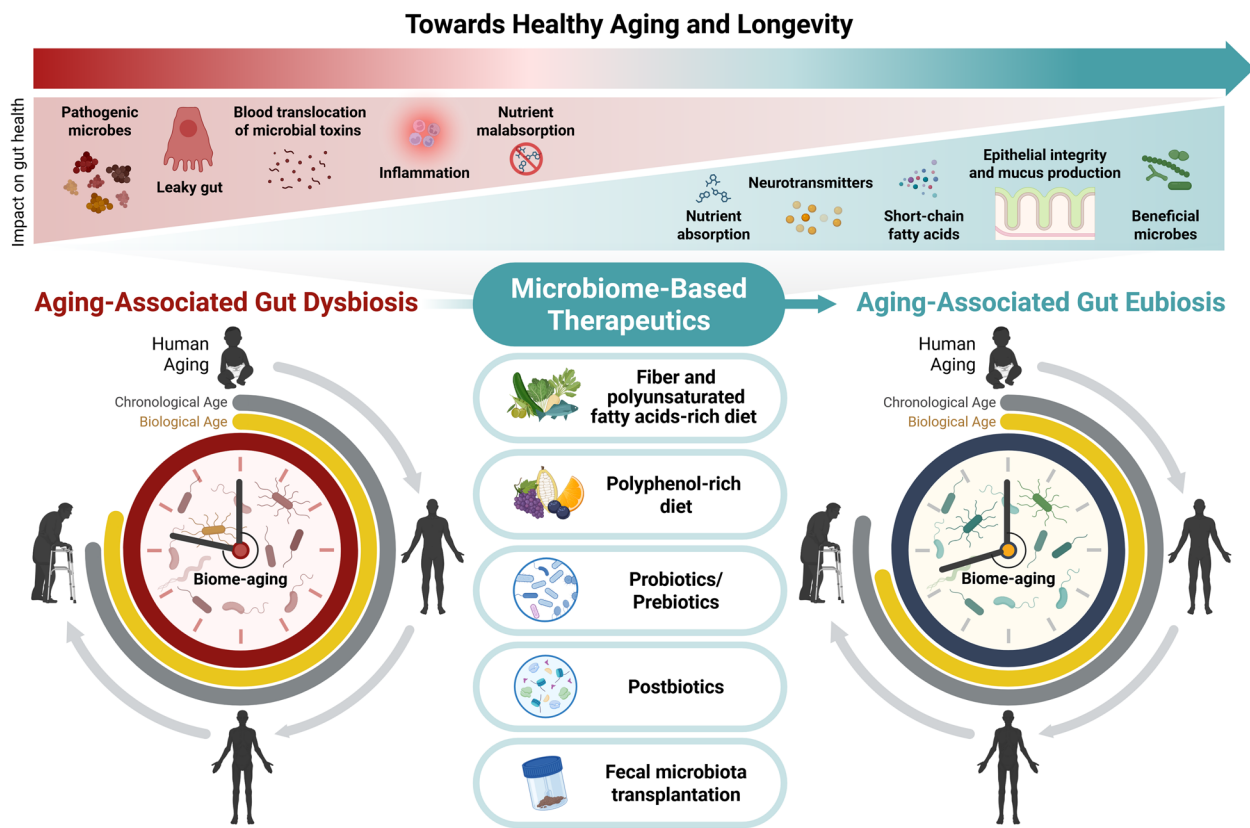


Fig. 1 Conceptual overview of biome-aging and microbiome-based therapeutics. As individuals age, significant changes in factors such as diet, lifestyle, and physiology contribute to a process termed “biome-aging”—an aging-associated gut dysbiosis characterized by the loss of beneficial commensals, proliferation of pathogenic microbes, and increased intestinal permeability (“leaky gut”). This dysregulated gut environment facilitates the translocation of microbial toxins into the systemic circulation, promoting chronic inflammation. Concurrently, the decline in functional microbes impairs nutrient metabolism and biosynthesis, leading to nutrient malabsorption and deficiencies in microbially derived essential nutrients. Together, these changes accelerate biological aging and increase the risk of age-related diseases. Microbiome-based therapeutic strategies—including fiber- and polyunsaturated fatty acid-rich diets, polyphenol-rich diets, probiotics, prebiotics, postbiotics, and fecal microbiota transplantation—show potential to mitigate biome-aging by restoring gut microbial balance. These interventions promote the proliferation of beneficial, functional microbes and the production of key microbially derived metabolites such as short-chain fatty acids and neurotransmitters. In turn, they support nutrient biosynthesis, enhance epithelial barrier integrity, and improve mucus production, thereby contributing to healthy aging and disease prevention. Created in BioRender. Nagpal, R. (2025) (<https://BioRender.com/5137mjt>)

cytokine and mucus production, thereby increasing susceptibility to pathogen invasion and infections [17].

With respect to the accessory organs, aging reduces pancreatic exocrine secretions, which destabilizes microbial homeostasis in the gut. Primary and secondary bile acids (BAs) also decrease with age, although the profiles of secondary BAs are significantly altered by the gut microbiome in older adults. Notably, centenarians exhibit a unique microbiome phenotype capable of producing secondary BAs (e.g., unique isoforms of lithocholic acid) with antimicrobial properties, promoting intestinal homeostasis and colonization resistance [18]. Conversely, dysbiotic profiles of microbiome-derived secondary BAs, such as deoxycholic acid and its glycine- or taurine-conjugated forms, have been associated

with aging-associated disorders including Alzheimer’s disease (AD) [19]. Taken together, perturbations in secondary BA profiles could be postulated as one of the mechanisms through which microbiome changes impact intestinal homeostasis and host aging-associated health. Furthermore, in conjunction with aging and systemic senescence, the gallbladder gradually develops insensitivity to the satiety-mediating peptide hormone cholecystokinin, leading to its elevated plasma levels [20]. This suppressed cholecystokinin function progressively leads to reduced appetite/hunger and food intake, and promotes malnutrition in older adults, all of which gradually diminish the beneficial gut microbes essential for vitamin synthesis, energy metabolism, and immune function [21]. Given that the intrinsic and extrinsic factors

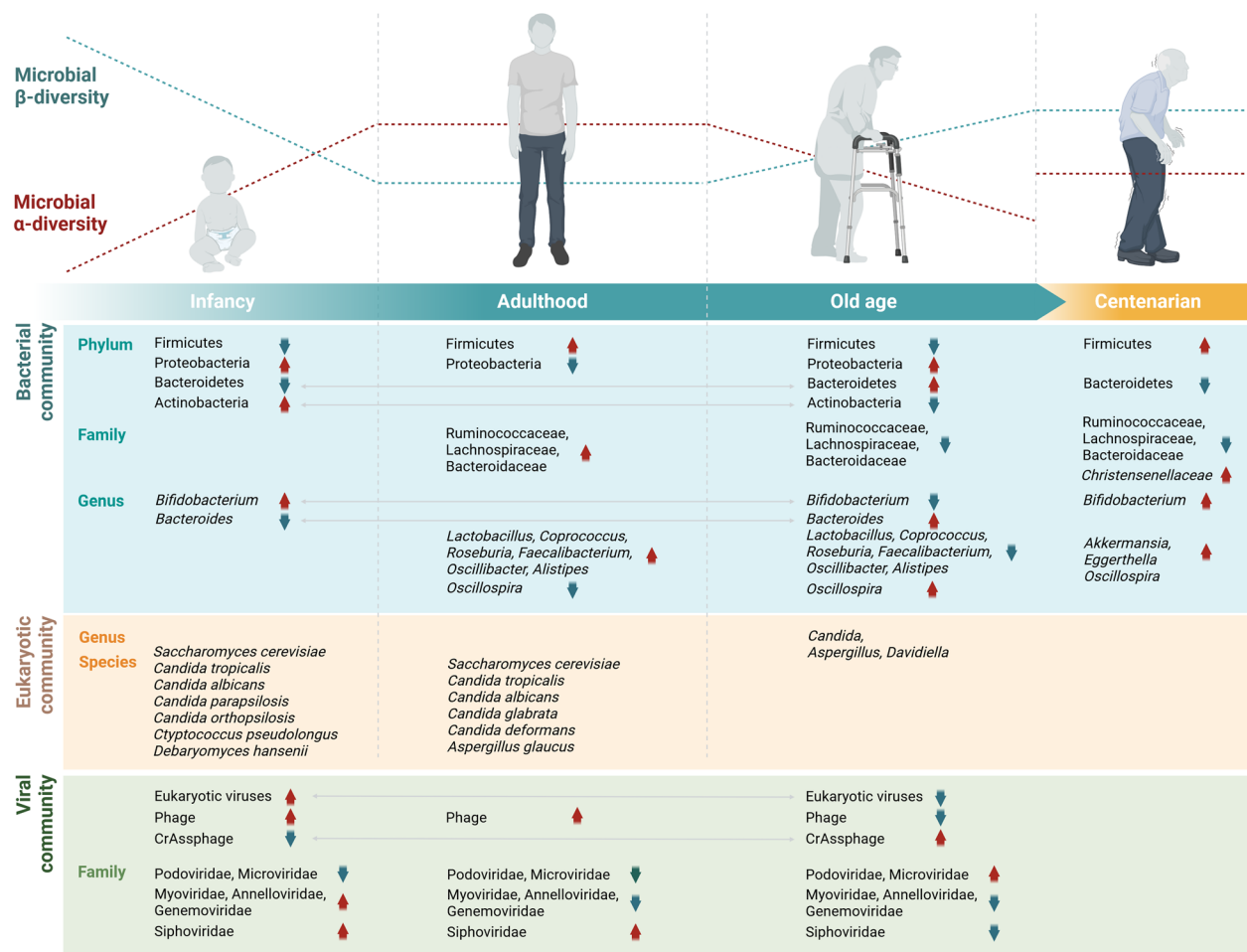


Fig. 2 Dynamic shifts in the gut microbiome composition across the lifespan. Changes in the intestinal bacterial, fungal, and viral communities from infancy to adulthood, old age, and centenarians. Created in BioRender. Nagpal, R. (2025) (<https://BioRender.com/dyakwuj>)

that can affect the microbiome and its host are extremely diverse and highly individualized, our understanding of the precise mechanisms and outcomes of biome-aging remains largely unclear. Nevertheless, emerging evidence is rapidly driving significant progress in the complex and vital investigation of gut microbiome–host physiological interactions. In the following section, we turn our attention to contemplating how these cumulative changes translate into observable microbial signatures that reflect, or potentially predict, host senescence and longevity.

Biome-aging signatures of host senescence and longevity

Gaining a comprehensive understanding of the biome-aging phenomenon holds tremendous promise as a tool to support healthy aging and longevity. As depicted in Fig. 2, our microbiome adapts steadily as we age through different stages of our lifespan. Although the existence of a prenatal intrauterine microbiome remains a topic of debate [22], it is well established that intestinal

colonization by commensal bacteria begins after birth [23]. This neonatal microecological ontogenesis continues to develop during infancy (the “first 1000 days” of life) and reaches relative stability by 3–4 years of age [23]. The newborn gut is dominated by *Bifidobacterium* spp.; however, the abundance of *Bifidobacterium* spp. tends to decline by the first year of life due to the introduction of other competitive microbial groups in association with weaning from breast milk or formula to the consumption of solid foods. While it was previously thought that the infant microbiome begins to exhibit an adult-like structure by 3–6 years of age [5, 24], recent studies suggest that certain microbiome features in children aged 6–12 years still differ significantly from those of adults [25]. In contrast, gut mycobiome (the fungal microbiome) development follows an inverse trend to bacteriome development, with fungal diversity and abundance decreasing as individuals transition into adulthood [26]. Neonatal and infant gut mycobiomes are typically dominated by

Saccharomyces and Exobasidiomycetes (birth), *Debaromyces hansenii* and *Candida parapsilosis* (3 months), and *Saccharomyces cerevisiae* (1 year) [26]. This developmental trajectory is influenced by a range of prenatal and neonatal factors, including delivery mode, feeding type, hospital environment, maternal microbiome, and antibiotic exposure. Breastfed infants harbor bifidobacterial species specialized in human milk oligosaccharide digestion, while formula-fed infants develop a more diverse microbiome [5]. Subsequently, the adult microbiome harbors a stable bacterial phylum profile dominated by Firmicutes and Bacteroidetes, followed by Actinobacteria, Proteobacteria, and Verrucomicrobia [23]. However, lower-level taxonomic variation remains high across individuals due to the diversity and density of the adult gut microbiome.

As global aging accelerates, research is increasingly focused on understanding microbial successions in later life to predict features of aging-related diseases and promote healthy aging. It has recently been discovered that the progression from young adulthood (22–48 years) to semi-supercentenarian status (105–109 years) is marked by a salient decrease in microbial clades belonging to the families Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae, while *Oscillospira*, *Akkermansia*, Christensenellaceae, and *Bifidobacterium* correlate positively with age [27]. Christensenellaceae in particular seems to be influenced by host genetics, with genotype explaining 30–40% of its abundance, suggesting a potential link between host genetics and human longevity through its promotion [28]. *Akkermansia muciniphila*, a prominent gut mucin degrader, has been found to maintain epithelial integrity while protecting against enteric inflammation and metabolic dysfunction [29]. *Bifidobacterium* spp. have been found to antagonize proinflammatory microbial taxa and contribute to SCFA production via cross-feeding mechanisms [23]. Although these taxa are linked to healthy living and longevity, it remains unclear whether this stems from lifestyle habits or is uniquely individual-specific. Nonetheless, restoring lost beneficial microbes could inform the development of interventions to promote healthy aging and longevity. The notion that longevity may be associated with key microbiome signatures is further corroborated by longitudinal studies reporting the preservation of higher microbial diversity and species richness in centenarians compared to older adults (age 66–85) [2], where, interestingly but not surprisingly, the intestinal carriage of *Bacteroides*—specifically, more beneficial commensal species such as *B. thetaiotaomicron* and *B. uniformis*—has been found to be markedly higher in centenarians. Another study linked healthy aging to a microbiome aging trajectory characterized by an age-dependent

decline in *Bacteroides* abundance and an increase in gut microbiome uniqueness, driven by rare taxa capable of synthesizing bioactive microbiota-derived metabolites such as indoles [3]. Notably, *Bacteroides* is a functionally diverse genus, with its species playing roles in both health and disease, as reviewed elsewhere [30]. Therefore, examining aging trajectories at the species level would offer deeper insights into aging microbiome dynamics. An ideal aging microbiome would support beneficial taxa while limiting frailty-associated pathobionts. Frailty presents with reduced grip strength, low energy, physical inactivity, and weight loss and consequently predisposes older adults to disability, hospitalization, and mortality. These criteria also correlate with the loss and/or gain of specific microbial taxa throughout the lifespan. For instance, a high frailty score has been associated with depletion of the intestinal population of specific commensal and beneficial taxa (*Coprococcus eutactus*, *Prevotella copri*) and dominance of potentially detrimental clades (*Clostridium hathewayi*, *Bacteroides fragilis*) [31]. Increased gut carriage of bacterial groups, including *Enterocloster bolteae*, *E. asparagiforme*, *Lacrimispora hathewayi*, *Clostridium citroniae*, *C. symbiosum*, and *Streptococcus parasanguinis*, has been associated with aging and reported as a characteristic of high frailty scores [4]. Mechanistically, these microbiome shifts are linked to metabolic alterations associated with ARDs, including reductions in SCFAs and tryptophan, alongside increases in threonine, hydrophobic secondary BAs (lithocholic acid and deoxycholic acid), trimethylamine oxide (TMAO), *p*-cresol, ethanol, and ammonia. Simultaneously, key fiber-fermenting taxa reliant on fructo- and xylo-oligosaccharides tend to decline [4]. Together, these findings support the biome-aging mechanism, where diminished microbial diversity, characterized by a gain in opportunistic/proinflammatory microbes and a decline in commensal/beneficial members, is implicated in accelerated aging and increased frailty. In the following section, we explore how such microbial imbalances—particularly those aligned with dysbiosis—may predispose aging individuals to a range of systemic diseases and chronic health conditions.

Biome-aging, gut dysbiosis, and associated disease predisposition

A growing body of research reveals a complex, bidirectional communication network between the gut microbiome and all organ systems, mediated primarily through endocrine, neural (e.g., vagus nerve), metabolic, and immune pathways. Whether in a state of dysbiosis or eubiosis, microbes influence the synthesis of SCFAs, neurotransmitters (gamma-aminobutyric

Table 1 Summary of evidence suggesting the role of aging-associated microbiome dysbiosis in different diseased states

Disorder/dysfunction	Microbiome alteration	Microbe–host interactions and metabolite effects	Reference
Colorectal cancer	<i>Fusobacterium</i> , <i>Parvimonas</i> , <i>Porphyromonas</i> , <i>Bacteroides</i> , <i>Gemella</i> , <i>Enterobacter</i> , <i>Peptostreptococcus</i> ▲	<i>Fusobacterium nucleatum</i> induces tumor signaling by binding to E-cadherin on tumor cell surfaces via adhesin (FadA), suppresses immunosurveillance by binding to lymphocytes, and increases chemoresistance in intestinal epithelial cells by upregulating TLR4 expression	[33, 34]
Inflammatory bowel disease	<i>Escherichia</i> , <i>Klebsiella</i> ▲ <i>Alistipes</i> , <i>Barnesiella</i> , <i>Faecalibacterium</i> , <i>Oscillibacter</i> , <i>Agathobacter</i> , <i>Roseburia</i> , <i>Ruminococcus</i> ▼	Putative role of reduced butyrate-producing taxa and enriched bacteria-derived virulence factors such as enterotoxin, hemolysins, invasion protein, and cytotoxic necrotizing factor in disease pathology	[32]
Inflammaging	<i>Ruminococcus</i> , <i>Clostridium</i> , <i>Prevotella</i> , <i>Allobaculum</i> , <i>Bifidobacterium</i> , <i>Oscillospira</i> , <i>Lactobacillus</i> , <i>Bacteroides</i> ▲ <i>Alistipes</i> , <i>Akkermansia</i> , <i>Blautia</i> , <i>Oscillibacter</i> , <i>Mucispirillum</i> ▼	▲Proinflammatory cytokines (TNFα, IL-6, IL-17A, and IL-1α) ▼Anti-inflammatory cytokines (IL-27) ▼Serum tryptophan levels	[36, 38]
Immunosenescence	Pathobionts (<i>Bacteroides</i> , acetogenic bacteria, Proteobacteria)▲ <i>Akkermansia muciniphila</i> , <i>Bacteroides fragilis</i> ▼	▼SCFAs leading to interference in immunological cell differentiation polarization, cytokine induction ▲OMV (from pathobionts such as <i>Salmonella typhimurium</i>) triggers activation of inflammasome complexes	[1, 39]
Cardiovascular disease	Enterobacteriaceae, <i>Prevotella</i> , <i>Hungatella</i> , <i>Succinoclasticum</i> , <i>Streptococcus</i> spp., <i>Solobacterium moorei</i> , <i>Atopobium parvulum</i> , <i>Eggerthella lenta</i> ▲ Lachnospiraceae, <i>Roseburia intestinalis</i> , <i>Bacteroides</i> spp., <i>Prevotella copri</i> , <i>Alistipes shahii</i> , <i>Faecalibacterium</i> , <i>Bifidobacterium</i> , <i>Blautia</i> , <i>Coprococcus</i> , <i>Fusicatenibacter</i> ▼	▼SCFAs ▲CD25 (a marker of T cell and macrophage activation) ▲TMA/TMAO ▲LPS ▲Secondary bile acids (lithocholic, deoxycholic, and ursodeoxycholic acid)	[41, 42]
Alzheimer's disease	Actinobacteria, Ruminococcaceae, Enterococcaceae, Lactobacillaceae, <i>Escherichia</i> , <i>Shigella</i> ▲ Bacteroidota, Negativicutes, Lachnospiraceae, Bacteroidaceae, Veillonellaceae, <i>Eubacterium rectale</i> ▼	▲TMAO ▲LPS ▲Bacterial amyloids ▲Proinflammatory cytokines	[46–48]
Parkinson's disease	Bifidobacteriaceae, Ruminococcaceae, Verrucomicrobiaceae, Christensenellaceae, <i>Bacteroides fragilis</i> , <i>Lactobacillus acidophilus</i> ▲ <i>Prevotellaceae</i> , Lachnospiraceae, <i>Faecalibacterium</i> ▼	▲TMAO ▼SCFAs, choline ▼Ghrelin	[49]
Physical frailty and sarcopenia	<i>Oscillospira</i> , <i>Ruminococcus</i> ▲ Barnesiellaceae, Christensenellaceae▼	▼Aspartic acid, threonine ▼Macrophage inflammatory protein 1α	[51]
Osteoporosis	<i>Clostridium</i> XIVa, <i>Coprococcus</i> , <i>Eggerthella</i> , <i>Bacteroides</i> , <i>Eisenbergiella</i> ▲ <i>Veillonella</i> ▼	▼SCFAs, thereby affecting regulation of calcium absorption and insulin like growth factor 1	[53]
Atopic dermatitis	<i>Alcaligenaceae</i> , <i>Bacteroides</i> , <i>Faecalibacterium</i> , <i>Oscillospira</i> , <i>Parabacteroides</i> , <i>Sutterella</i> ▲ <i>Actinomyces</i> , <i>Bifidobacterium</i> , <i>Blautia</i> , <i>Coprococcus</i> , <i>Enterococcus</i> , <i>Eggerthella</i> , <i>Eubacterium</i> , <i>Propionibacterium</i> ▼	▼SCFAs ▲Phenol, <i>para</i> -cresol	[100]
Multiple (type-2 diabetes, polyps, colorectal cancer, and autism)	<i>Enterocloster boltea</i> , <i>E. asparagiforme</i> , <i>Lacrimispora hathewayi</i> , <i>Clostridium citroniae</i> , and <i>C. symbiosum</i> ▲	▼SCFA, tryptophan ▲Threonine, TMA, <i>p</i> -cresol, ethanol, ammonia, and secondary bile acids	[4]

FadA *Fusobacterium* adhesin A, *TLR* Toll-like receptor, *TNFα* tumor necrosis factor alpha, *IL* interleukin, *SCFA* short-chain fatty acid, *OMV* outer membrane vesicle, *CD25* cluster of differentiation 25, *TMA* trimethylamine, *TMAO* trimethylamine *N*-oxide, *LPS* lipopolysaccharide

acid [GABA], dopamine, and serotonin), cytokines, lipopolysaccharides (LPS), hormones, neuropeptides, and amino acids. Disruptions in these gut–axis communications are increasingly linked to intestinal, immune, cardiovascular, and cognitive disorders (see Table 1 and Fig. 3).

Biome-aging and intestinal disorders

Intestinal disorders are closely linked with gut dysbiosis and associated cellular/molecular dysregulated signaling along this axis [6, 32]. Such microbiome aberrations often lead to gut epithelial hyperpermeability (“leaky gut”), reduced mucus production and mucosal immunity,

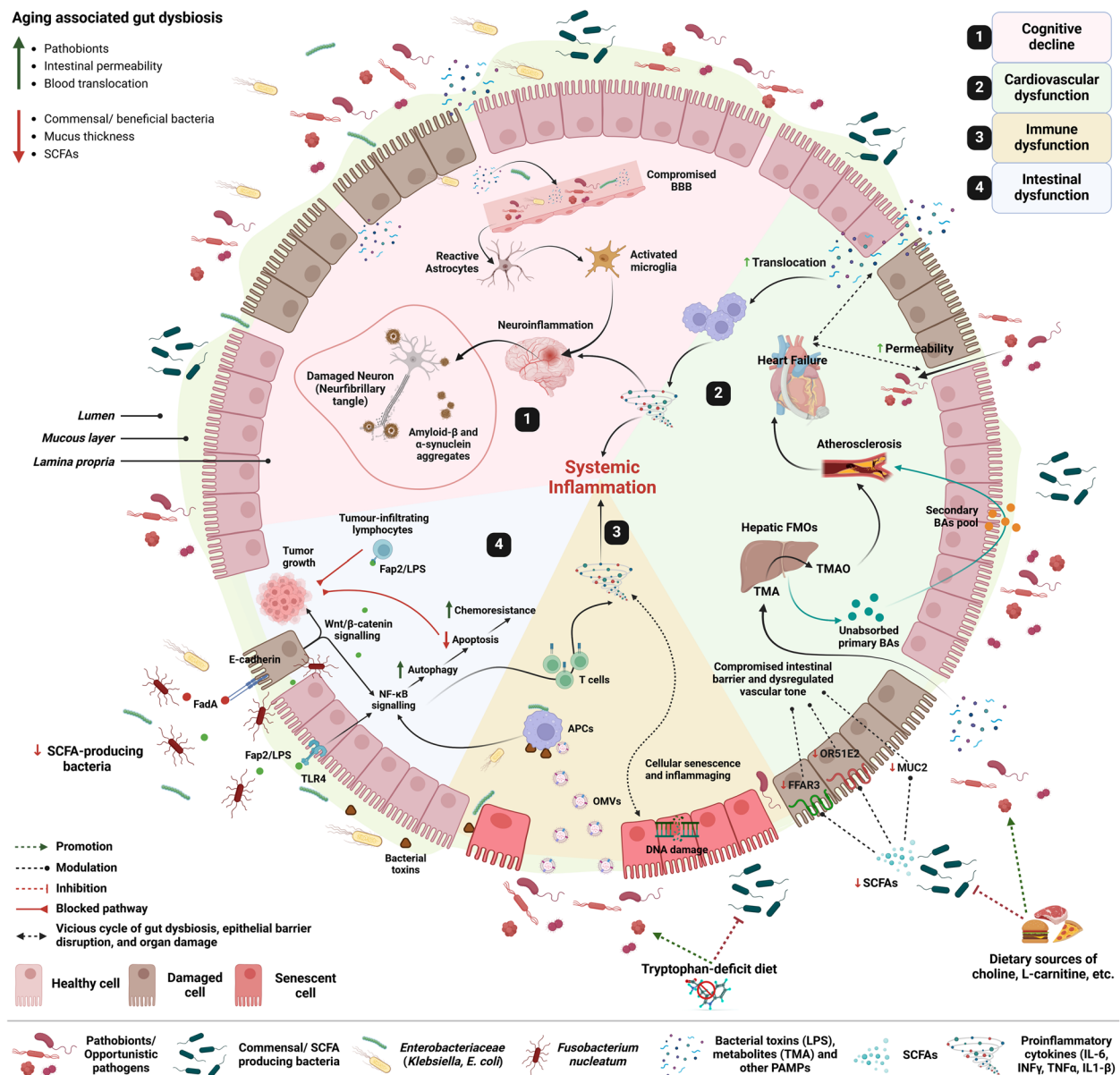


Fig. 3 An outline of mechanistic insights between gut dysbiosis and aging-associated disorders. Aging-associated gut dysbiosis is manifested by a gradual increase in the abundance of pathobionts and decrease in commensal/beneficial microbial taxa, leading to corresponding shifts in the metabolic pool (e.g., decreased SCFAs and increased harmful metabolites like TMA), with a concomitant increase in intestinal permeability, decrease in mucous production, and elevated blood translocation of microbes, their metabolites, and PAMPs: (1) These perturbations, via a compromised blood–brain barrier (BBB), increase the risk of cognitive disorders (Alzheimer’s and Parkinson’s disease) in the elderly by activating astrocytes and microglia, leading to neuroinflammation and formation of protein aggregates (β -amyloid/ α -synuclein) and tau atrophy. (2) Decreased production of SCFAs also adversely affects mucin production and disturbs modulation of blood vascular tone, posing a risk to cardiovascular health. Moreover, gut dysbiosis metabolism promotes harmful metabolites (e.g., TMA, secondary BAs), further aggravating the situation, leading to atherosclerosis, and finally heart failure. Heart failure induces intestinal ischemia and edema, which further fuels gut leakiness and indirectly heightens the pro-inflammatory response. (3) Inflammation and immunosenescence is promoted by gut dysbiosis via bacterial PAMPs, OMVs, etc., triggering the NF- κ B pathway and secreting proinflammatory cytokines, which in turn promote cellular senescence by delayed DNA damage repair mechanisms. (4) Promotion of certain bacterial species (e.g., *Fusobacterium nucleatum*) via their PAMPs (e.g., FadA, Fap2, LPS) interacts with receptors (TLR4, E-cadherin), thereby augmenting tumor signaling and suppressing autophagy, leading to the development of intestinal disorders like colorectal cancer. SCFAs, short-chain fatty acids; FadA/Fap2, *Fusobacterium* adhesins; TLR4, Toll-like receptor 4; NF- κ , nuclear factor kappa; Wnt, wingless/integrated pathway; LPS, lipopolysaccharide; OMVs, outer membrane vesicles; APCs, antigen-presenting cells; MUC2, mucin 2; OR51E2, olfactory receptor 51E2; FFAR3, free fatty acid receptor 3; TMA, trimethylamine; TMAO, trimethylamine N-oxide; FMOs, flavin monooxygenases; BAs, bile acids; PAMPs, pathogen-associated molecular patterns; IL, interleukin; INF, interferon; TNF α , tumor necrosis factor alpha. Created in BioRender. Nagpal, R. (2025) (<https://BioRender.com/5xg1c1b>)

and heightened pro-inflammatory responses—all implicated in enteric pathologies such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and colorectal cancer (CRC) [6]. For example, specific disease-associated taxa (e.g., *Fusobacterium*, *Parvimonas*, *Porphyromonas*, *Bacteroides*, *Gemella*, *Enterobacter*, and *Peptostreptococcus*) have been found to be abnormally increased in CRC patients [33]. *Fusobacterium nucleatum* promotes CRC progression by activating tumor signaling pathways, suppressing immunosurveillance, and enhancing chemoresistance and autophagy [34]. Furthermore, increased *F. nucleatum*, in concurrence with depleted diversity and butyrate/GABA biosynthesis, has been reported in patients with early-onset CRC [35]. The pathology of IBD has also been associated with the depletion of certain beneficial taxa (*Faecalibacterium* and *Roseburia*) and enrichment of pathobionts (*E. coli* and *Klebsiella*) and bacterial virulence factors [32], further underlining the plausible role of microbe-derived virulent factors in exacerbating disease severity. Future clinical and large-scale longitudinal studies are anticipated to reveal and validate deeper mechanisms underlying these gut disease hypotheses and observations.

Biome-aging and immune dysfunction

Inflammaging, characterized by chronic inflammation associated with aging, is regulated and exacerbated by several factors, including oxidative stress, immune cell senescence (immunosenescence), and gut dysbiosis. These factors collectively disrupt the functionality of the gut–immune axis, eventually intensifying aging-associated inflammatory processes [6, 11, 36]. Aging-associated microbial dysbiosis can stimulate intestinal epithelial permeability and macrophage dysfunction, which may in turn cause translocation of bacterial products into the bloodstream, thereby fueling systemic hyperinflammation (e.g., elevated TNF α levels) [36]. For instance, studies have demonstrated that fiber deficiency, which typically accompanies aging-related dietary shifts and reduced SCFA synthesis, results in gut dysbiosis along with increased abundance of mucin-degrading bacteria [37], leading to decreased mucosal layer thickness and increased pro-inflammatory cytokines (IL-33 and IL-25) and immunoglobulin E (IgE)-mediated immune responses [37]. Another example is tryptophan, which is a microbiome-derived metabolite indispensable for maintaining gut health and intestinal homeostasis. It was reported that a tryptophan-deficient diet may also induce gut dysbiosis and promote inflammaging in preclinical aged murine models [38]. Immunosenescence caused by degeneration of lymphocytes (e.g., CD4⁺ T cells) in patients with HIV has also been speculated to be induced by gut dysbiosis [39]. A recent study using microbiota

transplants from a postmenopausal participant before and after caloric restriction in gnotobiotic mice demonstrated how caloric restriction-associated microbiota promote naïve B and T cells while reducing effector memory cells, suggesting that caloric restriction may delay immunosenescence through the host immune–microbiota axis [40]. This is particularly important as the microbiome-mediated remodeling of the host immune system is governed by two key mechanisms—production of SCFAs and direct activation of innate immunity. Microbiome-derived SCFAs are known to modulate host immunity by influencing the differentiation and polarization of immune cells, activating G protein-coupled receptors (GPCRs), and inhibiting histone deacetylases [1]. Furthermore, the direct activation of innate immunity, particularly associated with the release of outer membrane vesicles (OMVs) by pathobionts, is also known to lead to macrophage dysfunction [1]. Together, these reports and mechanisms suggest how a “healthy” or “youthful” microbiome could play an anti-aging role in protection against senescence and inflammaging [6].

Biome-aging and cardiovascular disorders

A growing body of evidence reveals that gut dysbiosis plays a major role in promoting cardiovascular disease (CVD), heart failure, and atherosclerosis [41]. The gut–heart hypothesis postulates that cardiomyopathy-induced intestinal ischemia and edema promote leaky gut, causing an increase in bacterial components in the bloodstream and subsequent heightened inflammatory responses [42]. Inevitably, impaired intestinal function alters gut microbiota and metabolite profiles. For instance, gut microbiota-derived TMAO has consistently been correlated with increased risk of atherosclerotic CVD [43]. Furthermore, there is a positive correlation of the CD25 marker with heart failure, which is inversely associated with Lachnospiraceae [44]. Microbiome-derived SCFAs are also known to regulate blood pressure and vascular tone by modulating G-protein receptors (GPR41 and GPR43), activating olfactory receptor 51E2, upregulating histone acetyltransferases and histone deacetylases, and promoting mucus production. The production of trimethylamine (TMA)/TMAO and secondary BAs by gut microbial metabolism of choline, phosphatidylcholine, and L-carnitine has been linked to increased cardiovascular risk [42]. The gut-to-blood translocation of LPS under a hyperpermeable or “leaky” gut epithelial milieu is also known to promote atherosclerosis via TLR4/NF- κ B signaling-mediated proinflammatory cytokine secretion [41]. Gut microbes convert unabsorbed primary BAs into secondary BAs, which enter the enterohepatic circulation and may affect systemic inflammatory and

fibrotic processes [42]. Furthermore, oral microbiome dysbiosis, as seen in periodontitis, facilitates atherosclerotic plaque development by enabling translocation of pathogens (e.g., *S. mutans*, *Porphyromonas gingivalis*) into the systemic circulation, triggering inflammation and releasing pro-atherogenic toxins [45].

Biome-aging and cognitive disorders

The gut microbiome is also well known to exert an influence on neurocognitive function via the gut–brain axis. For instance, AD is a neurodegenerative disorder characterized by extracellular accumulation of amyloid- β plaques and intracellular deposition of neurofibrillary tangles of hyperphosphorylated tau proteins. This perturbed condition is avoided in the homeostatic state of astrocytes and microglia in brain parenchyma under gut eubiosis [46]. However, dysbiotic gut, due to compromised gut epithelial permeability and blood–brain barrier (BBB) integrity, may trigger hyperactivation of astrocytes and microglia by stimulating a proinflammatory cytokine storm induced by bacterial neurotoxins (e.g., LPS) and pathogens. Depleted gut microbial richness and an increased Firmicutes-to-Bacteroidetes ratio is commonly discovered in patients with AD [47], with increased population of specific pathogenic and proinflammatory bacterial genera (e.g., *Escherichia*, *Shigella*) and reduced commensal anti-inflammatory bacteria (e.g., *Eubacterium rectale*) in patients compared to healthy counterparts [48]. Parkinson's disease is another common disorder characterized by the loss of dopaminergic neurons in the substantia nigra compacta and the appearance of Lewy bodies (α -synuclein accumulation). Although patients with Parkinson's disease exhibit reduced abundance of butyrate-producing taxa (Prevotellaceae and Lachnospiraceae), a concomitant increase in certain beneficial taxa has also been reported (Bifidobacteriaceae, Ruminococcaceae, *Lactobacillus acidophilus*) [49], thereby complicating the findings of key taxa associated with Parkinson's pathology. However, an increase in beneficial taxa correlates with disease duration, as Ruminococcaceae is positively correlated with patients having > 10 years of disease history, but poor correlation was found with patients having < 10 years disease duration [50]. Additionally, choline, a precursor of two neurotransmitters (phosphatidylcholine and acetylcholine), has been found to decrease while TMAO levels in cerebrospinal fluid are increased in patients with neurocognitive disorders [49]. These findings further underscore the adverse consequences associated with the conversion of choline by the gut microbiome into the TMA/TMAO pathway.

Biome-aging and additional systemic health impacts

Biome-aging is also associated with aging-associated muscle, bone, liver, and skin health. Sarcopenia, a condition characterized by muscle wasting, appears to be affected by gut-microbial and gut-metabolite architecture [51]. Intestinal dysbiosis may alter skeletal muscle metabolism and promote muscle atrophy. Perturbations in the bidirectional crosstalk of the gut–liver axis with aging may predispose the host to hepatic dysfunction, leading to the genesis of geriatric nonalcoholic fatty liver disease (NAFLD) [52]. Bacterial groups that are found to prevail in patients with NAFLD include *Bacteroides* and *Ruminococcus*, whereas *Prevotella*, *Faecalibacterium*, *Akkermansia*, and *Bifidobacterium* have been found to be depleted [52]. Aging-associated skeletal abnormalities such as decreased bone mineral density and increased risk of fracture have also been linked to aberrant gut microbiota [53]. Perturbations in the gut microbiome may disturb skin function and contribute to dermatoses via the gut–skin axis. Decreased alpha diversity and alterations in gut microbiome composition and function, including reduced *Faecalibacterium prausnitzii* abundance and enrichment of GABA metabolism pathways, have been reported in elderly individuals with bullous pemphigoid, an autoimmune skin blistering disease [54]. Conversely, dermal injury may also influence the gut microbiome via the skin–gut axis, as demonstrated by Dokoshi et al. [55], showing that the release of dermal hyaluronan following skin injury altered the colonic microbiome, triggering colitis in experimental mouse models.

With this understanding, the next section will focus on how microbiome-based therapeutic interventions may counteract these aging-associated effects and promote healthy longevity.

Microbiome-based therapeutics to alleviate aging and promote longevity

Therapeutic interventions targeting the gut microbiome to restore eubiosis (homeostasis) from dysbiosis hold promise not only for improved gut health but also for overall health and promoting healthy aging and longevity by mitigating ARDs. Some of the recent discoveries and underlying mechanisms corroborating this premise are synthesized in Table 2 and Fig. 4 and are discussed in subsequent sections.

Nutritional and dietary elements

Among factors influencing gut microbiome and intestinal health, diet plays the most prominent role. While biological aging would inevitably lead to various physiological and microbial changes, several short-term and long-term dietary intervention studies have

Table 2 Summary of studies highlighting microbial interactions and metabolic effects of microbiome-based therapeutics

Category	Therapeutics	Microbial interactions and metabolic effects	Effect	Reference
Food and diet	Mediterranean diet	Enterobacteriaceae, Erysipelotrichaceae, Christensenellaceae, <i>Akkermansia</i> , <i>Slackia</i> , <i>Eubacterium</i> , and <i>Roseburia</i> ▲	SCFAs, BCFAs▲ Secondary bile acid, <i>p</i> -cresols▼	Pathway abundance linked to Alzheimer's disease▼
	Polyphenols	Bacteroidetes/Firmicutes ratio, <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Blautia</i> ▼ Lachnospiraceae, <i>Roseburia</i> , <i>Bacteroides</i> ▲	Polyphenol absorption, carnitine▲	Saturated fatty acid metabolism▲ bile acid metabolism▲
Probiotics, prebiotics, and synbiotics	Anthocyanin	Clostridiaceae-1, <i>Lactobacillus</i> , <i>Bacteroides</i> , S24-7, <i>Lachnospiraceae</i> NK4A136, <i>Aspergillus oryzae</i> ▲ Verrucomicrobia, Euryarchaeota▼	SCFAs▲	Mucosa damage▼
	Red ginseng	Bacteroidetes/Firmicutes ratio, Proteobacteria▼ <i>Lactobacillus</i> , <i>Akkermansia</i> ▲	Bioactive ginsenosides metabolites▲	Oxidative damage, Neural damage▼
Probiotics, prebiotics, and synbiotics	Probiotics combination	<i>Oscillospira</i> , <i>Allobaculum</i> , <i>Roseburia</i> , <i>Desulfovibrio</i> , <i>Dorea</i> ▲ <i>Akkermansia</i> , S24-7, <i>Lactococcus</i> , <i>Ruminococcus</i> , <i>SMB53</i> , <i>Coprobacillus</i> , <i>Lactobacillus</i> ▼	Bile salt hydrolase activity, taurine▲	Gut permeability▼
	GOS	<i>Bacteroides</i> , <i>Lactobacillus</i> , <i>Bifidobacterium</i> ▲ <i>Clostridium</i> ▼	β-galactosidases, SCFAs▲ BCFAs, Iso-butyrate, Iso-valerate▼	Mucus thickness▲ Gut permeability, inflammatory markers▼
Probiotics, prebiotics, and synbiotics	Synbiotic MPRO3	<i>Bifidobacterium</i> , <i>Faecalibacterium</i> , <i>Fuscatenibacter</i> , <i>Ellagibacter</i> ▲ <i>Blautia</i> , <i>Eubacterium_g5</i> , <i>Terriporobacter</i> ▼	High-density lipoprotein cholesterol▲ Body mass index▼ Creatine▼ C-reactive protein▼ Triglycerides▼	Bowel health▲
	Probiotics combination	Bacteroidetes/Firmicutes ratio, Proteobacteria, <i>Pseudomonas</i> , <i>Lachnospiraceae</i> NK4A136, <i>Alisities</i> , <i>Prevotella</i> ▼ <i>Eubacterium</i> , <i>Prevotellaceae</i> , <i>Allisonella</i> ▼	Gut permeability, blood-brain barrier injury▼	Neuroinflammation, oxidative DNA damage▼
Probiotics, prebiotics, and synbiotics	<i>Bifidobacterium</i> spp.		Antagonism against proinflammatory bacteria▼	Brain-derived neurotrophic factor▲ Histamine▼
				Mental flexibility▲ Stress▼

Table 2 (continued)

Category	Therapeutics	Microbial interactions and metabolic effects	Effect	Reference
Postbiotics	Urolithin B	Firmicutes/Bacteroidetes ratio, <i>Roseburia</i> , <i>Faecalibacterium</i> ▲ <i>Helicobacter</i> , <i>Parasutterella</i> ▼	Proinflammatory cytokines▼ HMGB1-TLR4-NF-κB pathway▼ Reactive oxygen species▼	[82]
		Verrucomicrobiaceae, Verrucomicrobiales, Verrucomicrobiae, <i>Akkermansia</i> ▲ <i>Actinobacteria</i> , Adlercreutzia, Coriobacteriales, Coriobacteriales▼	Mucin production▲ Inflammatory markers▼	
			Physical and metabolic function▲ Memory loss▼	
Drugs and supplements	Lipoteichoic acid			[10]
Drugs and supplements	Indole	Proliferation of epithelial cells, goblet cell differentiation▲ Epithelial homeostasis▲ Gut permeability▼	Systemic inflammation▼	[81]
		S24-7, <i>Ruminococcaceae</i> , <i>Lactococcus</i> ▲ Coriobacteriaceae, Veillonellaceae, <i>Lactobacillus</i> , <i>Dorea</i> , <i>SMB53</i> , <i>Roseburia</i> , <i>Dehalobacterium</i> ▼	Mucin expression▲ Inflammation, gut permeability▼	
			Metabolic dysfunction, cognitive dysfunction▼	
Drugs and supplements	Metformin			[7]
Drugs and supplements	Senolytic drug	Bacteroidetes/Firmicutes ratio, <i>Akkermansia</i> , <i>Ruminococcus</i> , <i>Oscillospira</i> , <i>Dorea</i> , <i>Sutterella</i> ▲ <i>Lactobacillus</i> ▼	Intestinal senescence, inflammation▼	[9]
			Health span, survival in aged subjects▲	
Drugs and supplements	Omega-3 fatty acid	<i>Bifidobacterium</i> , <i>Desulfovibrio</i> ▲ <i>Clostridia</i> sensu stricto 1, Vadin BB60 group, <i>Tyzzerella</i> , <i>Lachnospirillum</i> ▼	Acetate▲ Trimethylamine N-oxide▼	[87]
			Inflammatory markers▼	
			Age-associated thrombotic event▼	
Fecal microbiota transplantation	Young donor → old/germ-free	<i>Bifidobacterium</i> , <i>Alistipes</i> , <i>Turicibacter</i> , <i>Clostridium</i> , <i>Andarostipes</i> ▲ <i>Bacteroides</i> , <i>Prevotella</i> ▼	SCFAs▲	[94]
			Gut integrity▲	
			Behavioral impairment, brain/gut inflammation▼	
Fecal microbiota transplantation	Long-living donor	<i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Roseburia</i> , <i>Faecalibacterium</i> , <i>Ruminococcus</i> , <i>Coprococcus</i> ▲	Intestinal villi▲ Lipofuscin, β-galactosidase▼	[95]
Fecal microbiota transplantation	Healthy young donor	<i>Bacteroidales</i> , <i>Bacteroidia</i> , <i>Tannerellaceae</i> , <i>Actinobacteria</i> ▲	SCFAs▲	[93]
			Pentose phosphate cycle▲	
			Dementia▼ (case study)	

SCFA short-chain fatty acid, BCFA branched-chain fatty acid, GOS galactooligosaccharide

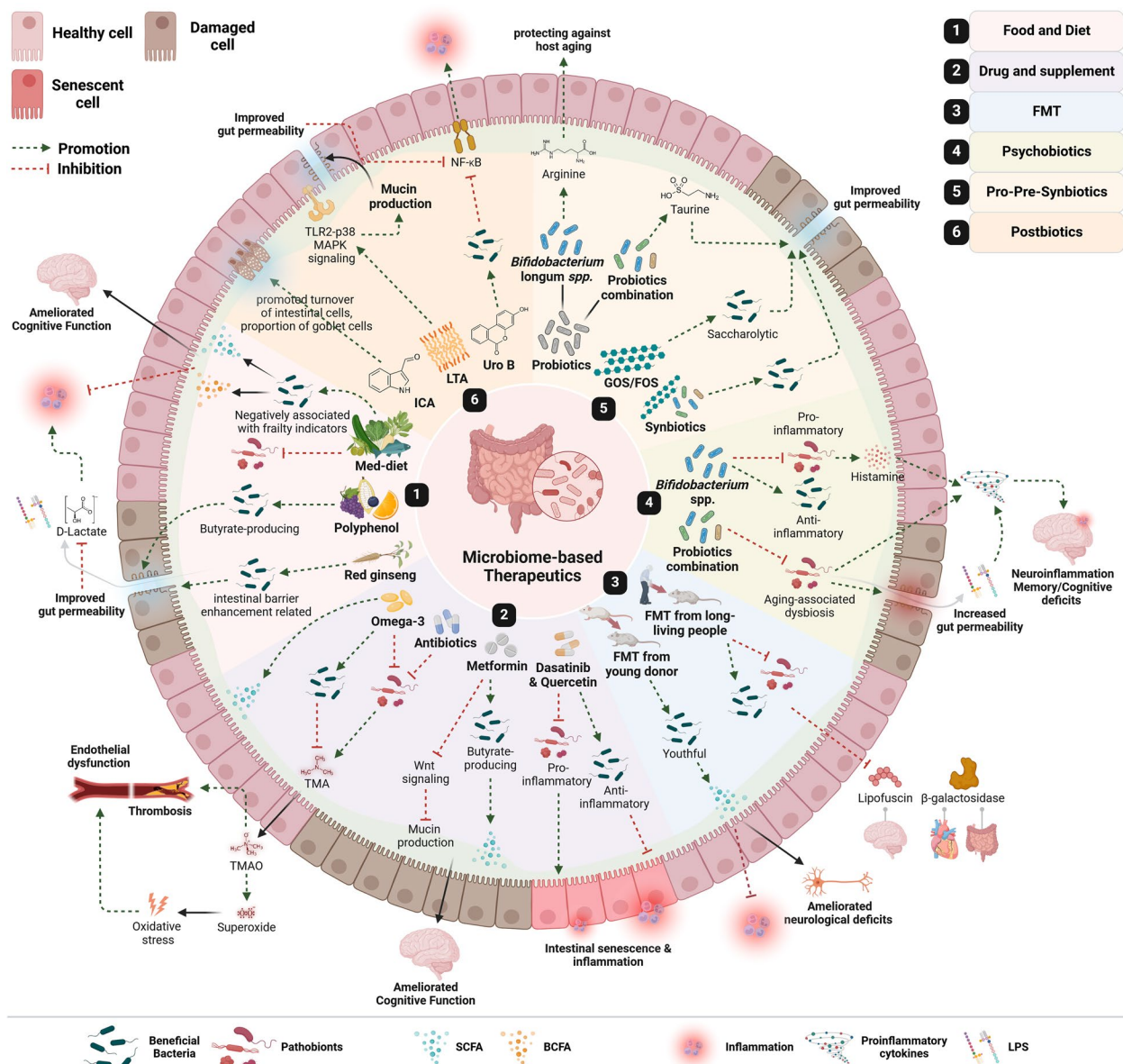


Fig. 4 Potential microbiome-based therapeutics to prevent unhealthy aging and nurture healthier disease-free aging and longevity. With the recognition of the crucial role of the gut microbiome in aging-associated disorders, microbiome-based therapeutics for ameliorating or preventing aging-associated disorders are being actively studied. These therapeutics are designed to restore or promote the beneficial microbiota and its function or reduce pathobionts, thereby rebalancing the gut microbial community and breaking the cycle of disorders. A range of therapeutics have been demonstrated, including consumption of specific diets or food, supplementation with probiotics, prebiotics, synbiotics, postbiotics, drugs, and supplements, and transfer of the gut microbiota. BCFA, branched-chain fatty acid; FMT, fecal microbiota transplant; FOS, fructooligosaccharide; GOS, galactooligosaccharide; ICA, indole-3-carboxaldehyde; LTA, lipoteichoic acid; Med-diet, Mediterranean diet; NF-κB, nuclear factor kappa B; SCFA, short-chain fatty acid; TLR2, Toll-like receptor 2; MAPK, mitogen-activated protein kinase; TMA, trimethylamine; TMAO, trimethylamine *N*-oxide; Uro B, urolithin B. Created in BioRender. Nagpal, R. (2025) (<https://BioRender.com/heaxrmr>)

demonstrated considerable potential to mitigate senescence-associated morbidity and mortality. For instance, a long-term and large-scale clinical study (ClinicalTrials.gov identifier NCT01754012) established a close association of a prudent Mediterranean-style dietary pattern

with reduced frailty via microbiome modulation [56]. Frailty indicators were found to be negatively correlated with the abundance of several gut commensals including *F. prausnitzii*, *Roseburia hominis*, and *Eubacterium* spp., while showing a positive correlation with potential

pathobionts (*Ruminococcus torques*, *Collinsella aerofaciens*, *Clostridium ramosum*, and *Veillonella dispar*) previously linked to different pathophysiologies (e.g., type 2 diabetes, CRC, IBD). Similarly, our recent intervention trial (ClinicalTrials.gov identifier NCT02984540) with a modified Mediterranean-ketogenic diet (MkD) in older adults with mild cognitive impairment induced notable changes in specific microbial metabolites (increased propionate and butyrate) via gut microbiome modulation [8], where fecal propionate and butyrate correlated negatively with AD biomarkers. Our subsequent mechanistic studies investigating the cellular/molecular effects of MkD on the gut microbiome–brain axis in preclinical models revealed upregulation of gut microbiota-derived lactate levels and lactate receptors that mediate neuroprotective effects through modulation of hippocampal inflammasome pathways [57]. Another interventional study (ClinicalTrials.gov identifier NCT02984540) with a similar MkD dietary pattern in prediabetic adults with mild cognitive impairment also reported beneficial effects attributed to increased levels of GABA, which is influenced by gut microbes such as *Alistipes* sp. CAG:514 and *A. muciniphila* [58].

Dietary polyphenols are another functional dietary component well known for their antioxidant, anti-inflammatory, and neuroprotective effects and potential to prevent/ameliorate chronic conditions such as epilepsy, Parkinson's disease, cancer, CVD, diabetes, and neurodegenerative processes. Although the structural complexity and glycosylation of polyphenols limit their therapeutic potential owing to their reduced absorption in the small intestine, polyphenols accumulated in the large intestine have been found to modulate the microbiome composition through antimicrobial effects or prebiotic-like action of metabolites generated through polyphenol metabolism in the colon. For instance, the intake of diets rich in anthocyanin [59] and procyanidin B2 [60] is known to increase butyrate-producing bacteria and alleviate age-associated changes in aging rodent models. Furthermore, a polyphenol-rich diet, supplemented with specific probiotics, was found to alleviate chronic low-grade inflammation, thereby reducing biological inflammaging, accompanied by an increase in probiotic bacteria and SCFAs in the gut microbiome of adults aged 50 years and older [61]. Likewise, red ginseng, an herb rich in antioxidants, may confer anti-aging effects by reducing oxidative stress and promoting beneficial gut bacterial taxa, and through metabolic pathways associated with intestinal barrier enhancement [62]. Studies with specific probiotic-fermented ginseng interventions have also demonstrated anti-aging properties attributed to upregulation of specific genes linked to antioxidant activity and positive modulations in gut microbiome communities [63]. Thus,

it has been well established that adherence to prudent and balanced dietary patterns abundant in fiber, mono-/poly-unsaturated fatty acids, and polyphenols provides enduring advantages for intestinal, cardiometabolic, and neurocognitive health, at least partly if not exclusively by fostering a healthier microbiome.

Probiotics, prebiotics, and synbiotics

Emerging evidence suggests that specific probiotics, prebiotics, and synbiotics can enhance immune, intestinal, and metabolic health by restoring gut homeostasis and function [64–66]. This body of evidence also points to the positive effect of these pro/prebiotics on gut microbial and epithelial health in an aging gut milieu. For instance, studies have reported alleviation of aging-associated behavioral impairments linked to perturbations of arginine flux in aged mice by administration of specific arginine biosynthesis pathway-positive genotypes of *Bifidobacterium longum* strains, including 278, RG4-1, and FJSWXJ10M2 [67]. Similarly, in our recent study using aged mice, we reported that the administration of a human-origin probiotic cocktail containing *Lactobacillus* (*L. paracasei* D3-5, *L. rhamnosus* D4-4 and D7-5, and *L. plantarum* D6-2 and D13-4) and *Enterococcus* (*E. raffinosus* D24-1, *E. INBio* D24-2, and *E. avium* D25-1, D25-2, and D26-1) strains led to increased abundance of specific beneficial/commensal gut bacteria and microbial metabolites [65]. These positive changes correlated with improved gut epithelial integrity and reduced inflammasome activation and were subsequently found to be modulated by metabolites including SCFAs and taurine [65]. A similar study found that specific probiotic strains (*L. fermentum* SX-0718, *L. casei* SX-1107, *B. longum* SX-1326, and *B. animalis* SX-0582) isolated from the feces of centenarians led to improved intestinal epithelial integrity and reduced systemic inflammation in aged mice [66]. Furthermore, certain probiotic strains have also demonstrated a positive influence on the host neuropathology via modulation of the gut–brain axis. These strains, known as “psychobiotics,” may improve psychological health by modulating gut–brain interactions. Several recent studies investigating gut microbiome modulation via psychobiotic supplementation have reported improvement in specific clinical manifestations and behavioral outcomes. For example, a study (CRIS: KCT0003929) examining the consumption of probiotics containing *B. bifidum* BGN4 and *B. longum* BORI reported improved overall mental health in older adults (> 65 years) by suppressing proinflammatory and fostering anti-inflammatory gut microbes and cytokines and upregulating brain-derived neurotrophic factor (BDNF) pivotal to hippocampal synaptic plasticity and cognition [68]. Clinical studies have also reported improved

mental health, specifically related to anxiety, depression, and neuropsychiatric symptoms, attributed to probiotic intervention and an associated increase in the population of *F. prausnitzii*, a prominent fiber-degrading and SCFA-producing gut bacterium [69]. Studies using senescence-accelerated aging mouse models have also reported positive microbiome modulation in terms of reduced population of potential pathobionts, which were otherwise increased with aging, and improved gut epithelial and blood–brain barrier permeability after the administration of a probiotics mixture [70].

Recently, prebiotics (e.g., dietary fiber, resistant starches, galacto-/fructo-oligosaccharides) have also been gaining notable research and public health interest due to their holistic and positive impact on the gut microbiome composition and function. Prebiotic galactooligosaccharide administration has been found to modulate gut homeostasis in an aged gut by restoring and enhancing the abundance of saccharolytic bacteria and enzymes (β -galactosidases) and improving intestinal epithelial integrity and mucus production [71]. Moreover, resistant starches have been found to confer prebiotic effects, demonstrating the potential for precise modulation of the microbiome [72]. For example, in our recent studies, we have shown that resistant starches induce strong modulations in the gut microbiome and metabolome in aging mice, but the profiles of these modulations vary depending on specific resistant starches extracted from different types of food sources [64, 73, 74]. Studies have also explored synergistic and/or complementary attributes of synbiotic combinations for alleviating age-related complications. A clinical study reported positive modulations in blood metabolite profiles, gut microbiome, and overall bowel health in older women following the intake of a synbiotic product MPRO3 composed of probiotics (*B. animalis* spp. *lactis* HY8002, *L. casei* HY2782, and *L. plantarum* HY7712) and various dietary fibers [75]. Although the majority of research has been based on traditional probiotics including *Lactobacillus* and *Bifidobacterium* spp., there is increasing interest in exploring the health-beneficial aspects of specific newly discovered gut commensals such as *A. muciniphila*, *F. prausnitzii*, *Ruminococcus bromii*, *Anaerobutyricum hallii*, and *Roseburia intestinalis*, which are speculated to have great potential as next-generation probiotics (NGPs) [76]. Among these, *A. muciniphila* and *F. prausnitzii* are specifically emerging as noteworthy NGPs and are believed to play a role in mitigating age-related degeneration. Studies have indicated that patients with AD or mild cognitive impairment tend to exhibit lower levels of *F. prausnitzii*, and administration of *F. prausnitzii* isolated from healthy subjects has been shown to improve cognitive impairment in AD mouse models [77]. Furthermore, administration of both

A. muciniphila and *F. prausnitzii* has been demonstrated to ameliorate features of muscular atrophy by reducing myostatin, an inhibitor of skeletal muscle growth [78]. However, despite several randomized clinical trials conducted with pro/prebiotics in population cohorts aged 65 years or older, further and larger trials are needed and awaited to understand the precise effects and mechanisms of these supplements, particularly given the high inter-individual variability in microbiome composition, colonization resistance, and variation in microbiome responses to such interventions [79].

Postbiotics

Mounting interest and mechanistic evidence pertaining to the health effects of probiotics and prebiotics has recently led to the emergence of a new biotic class, called “postbiotics,” which specifically refer to microbial metabolites, cellular components, and/or intact but nonviable microbes (typically probiotic) that confer health benefits [80]. Many health effects of probiotics are mediated through their cellular fractions or metabolites, allowing for therapeutic use of these components without live bacteria. For example, we recently reported how the extracted cell wall component lipoteichoic acid (LTA) from a heat-killed probiotic strain *L. paracasei* D3-5 is sufficient to reduce inflammation through NF- κ B inhibition and gut epithelial hyperpermeability by enhancing mucin production via upregulating the TLR2-p38 MAPK signaling pathway [10]. Another study identified the postbiotic potential of indole or its derivative indole-3-carboxaldehyde (ICA), secreted by commensal microbiota, in ameliorating aging-associated health, presumably via high turnover of intestinal cells and enrichment of goblet cells via the aryl hydrocarbon receptor [81]. Recently, urolithin B (Uro B), a gut microbial metabolite derived from ellagitannins, was found to improve intestinal function by downregulating the HMGB1-TLR4-NF- κ B pathway, mitigating oxidative stress and positively modulating the gut microbiome in a D-galactose-induced aged model [82]. Heat-killed secretory components and cell surface proteins of specific *Lactobacillus reuteri* strains have also been found to confer positive effects on intestinal epithelial barrier functioning and the pathobiome in in vitro trials [83]. In addition, tyndallized forms of *B. longum* and *L. acidophilus* strains, in combination with exercise intervention, were recently found to aid in ameliorating AD pathologies, such as amyloid-beta aggregates, by downregulating amyloid-beta precursor protein (APP) gene expression and improving mitochondrial function [84]. On the basis of these emerging and mechanistic studies, future research on postbiotics is highly anticipated to offer promising avenues for developing novel

therapeutics or adjunct healthcare products to prevent/ameliorate ARDs.

Microbiome-associated drugs and supplements

Although antibiotics are well known to perturb gut microbiota composition and diminish microbial diversity, some specific drugs (e.g., metformin) may exert pleiotropic effects, particularly in older adults through their metabolism (or biotransformation) by the gut microbiome [85]. For instance, in a study using aging mouse models, we recently showed that metformin treatment enhances intestinal mucin production by suppressing Wnt signaling and the expression of Muc2 and goblet cell differentiation genes (*Spdef*, *Atoh*, and *Gfi*), thereby ultimately influencing neurocognitive function [7]. In a similar study, we also showed that specific senolytic drugs, i.e., dasatinib and quercetin, reduce intestinal senescence and inflammation likely by promoting anti-inflammatory and restricting pro-inflammatory gut microbes in aged mice [9]. Such findings suggest that the anti-aging effects of senolytic drugs might be at least partly intermediated via microbiota modulation.

Dietary supplements, widely available for addressing nutrient deficiencies and overall wellness, are commonly used, especially among older adults, who face higher deficiency risks due to age-related declines in digestion, metabolism, and immunity [86]. However, recent studies show that gut microbiome modulation may underlie the anti-aging effects of these ingredients. For example, plant-derived α -linolenic acid (ALA) was shown to confer antithrombotic effects and decrease platelet hyperresponsiveness in a mouse model of aging [87]. The study showed that the ALA-rich diet modulated the microbiome, restored acetate levels, and decreased plasma TMAO levels by re-establishing TMA-reducing microbes (*Rikenellaceae*_RC9_group and *Intestinimonas* sp.) and reducing TMA/TMAO-associated microbes (*Desulfovibrio* and *Clostridium*) [87]. In addition, nicotine has been identified to influence age-related symptoms by activating NAD⁺ pathways and rebalancing NAD⁺ homeostasis [88]. Similarly, nicotinamide adenine dinucleotide (NMN) administration has been shown to confer beneficial effects against age-related disorders, such as arterial stiffness, by maintaining NAD⁺ levels in organs and tissues [89, 90]. Although these studies did not investigate the role of the microbiome in these anti-aging effects, it is noteworthy that NMN is known to help maintain gut homeostasis by regulating the gut microbiome. Furthermore, given that the gut microbiome possesses unique enzyme activity, which mammalian hosts otherwise lack, contributing to NAD⁺ metabolism, the anti-aging effects of nicotine or NMN are hypothesized to be directly or indirectly associated with changes in the gut microbiome.

Nevertheless, further comprehensive, mechanistic, and translational studies are needed to validate and provide insight into this potential association [91, 92].

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is an emerging strategy for preventing and treating aging-associated diseases. While successful in treating recurrent *C. difficile* infections and conditions like IBS, Crohn's disease, and ulcerative colitis, FMT also shows potential in promoting healthier aging and longevity. For example, one study found that FMT improved cognitive function in older adults with AD by modulating the gut microbiome and enhancing SCFA production [93]. Preclinical studies have shown that FMT treatment leads to improvements in aging-associated neurological deficits and inflammation with enhanced SCFA concentration and expression of mucin genes in aged mice [94]. Subsequent studies have validated these results via supplementation with SCFA-producers (*B. longum*, *Clostridium symbiosum*, *F. prausnitzii*, *L. fermentum*), eventually indicating a bottom-up (from gut to brain) signaling approach leading to enhanced post-stroke recovery. Studies have also demonstrated that FMT from long-lived elderly donors into mice improves aging-related indices by promoting beneficial bacteria and metabolites [95]. On the basis of this evidence, systematic exploration of the use of healthy, long-lived donors to develop a well-characterized FMT biobank may offer an effective therapeutic avenue for mitigating aging-related health impairments.

Future directions

Despite substantial progress in research linking the gut microbiome to healthy aging and implicating dysbiosis and biome-aging in geriatric disorders, the precise role of specific microbial taxa and microbiome-derived metabolites in healthy aging and longevity remains elusive—particularly whether and which of these microbiome signatures are innate or shaped by lifestyle. A precise, personalized understanding of a “healthy” microbiome—while minimizing the impact of inter-individual variability—requires large-scale longitudinal studies across diverse demographics in order to predict biome-aging trajectories and systemically evaluate microbiome-targeted interventions [2, 96, 97]. The establishment and expansion of comprehensive microbiome biobank projects through global research consortia and collaborative networks will accelerate the collection of well-characterized microbial samples from diverse age groups, healthy centenarians, individuals with varying lifestyles, and populations from different geographical and socioeconomic backgrounds. This will provide a robust reference framework to identify universal and unique microbial

signatures associated with healthy aging and disease states.

Additionally, clinical research studies must go beyond assessing therapeutic efficacy to incorporate mechanistic explorations through the integration of advanced multi-omics technologies—such as metagenomics, metabolomics, meta-transcriptomics, and metaproteomics—to decipher how microbiome-derived cellular/molecular pathways influence cellular senescence, inflammation, and metabolic regulation. These investigations will be further strengthened by mechanistic validation in relevant experimental animal models, particularly germ-free or gnotobiotic systems, which provide powerful platforms for testing causality behind associations identified in human data [98, 99]. To support and scale these efforts, advanced computational approaches—including artificial intelligence (AI) and machine learning (ML)—should be employed to integrate complex microbiome datasets with clinical outcomes, environmental exposures, and host genetic profiles. These tools will enhance our ability to identify predictive biomarkers, map key microbiota–host interaction networks, and design personalized therapeutic strategies. Collectively, these integrated, system-level approaches will accelerate translational research and pave the way for microbiome-informed clinical solutions that promote healthy aging and extend the healthspan.

Conclusions

Research on aging biology is inherently complex due to the multifaceted nature of senescence. Although cellular, molecular, genetic, and epigenetic factors independently or collectively drive the senescence process, the past decade in particular has witnessed a surge of compelling studies highlighting both the direct and indirect roles of the gut microbiome in aging and ARDs—establishing a foundation for promising microbiome-based therapeutic strategies. Innovative microbiome-modulating strategies, including microbiota-modulating diets, FMT biobanks from healthy youthful or centenarian donors, and tailored probiotics/prebiotics/postbiotics, show potential in mitigating biological aging. With the increasing precision of advanced, high-throughput multi-omics technologies—coupled with AI and ML—future research is well positioned to disentangle the associative and causal roles of gut microbiome signatures and biome-aging mechanisms in biological aging. These insights are projected to significantly contribute to efforts aimed at enhancing the healthspan and achieving disease-free longevity.

Abbreviations

AD	Alzheimer's disease
AI	Artificial intelligence
ALA	Alpha-linolenic acid
APP	Amyloid-beta precursor protein
ARDs	Age-related diseases
BA	Bile acids
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
CRC	Colorectal cancer
ENS	Enteric nervous system
FMT	Fecal microbiota transplantation
GABA	Gamma-aminobutyric acid
GIT	Gastrointestinal tract
GPCRs	G protein-coupled receptors
ICA	Indole-3-carboxaldehyde
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IECs	Intestinal epithelial cells
IL	Interleukin
LPS	Lipopolysaccharides
MkD	Modified mediterranean-ketogenic diet
ML	Machine learning
NAD	Nicotinamide adenine dinucleotide
NF- κ B	Nuclear factor kappa B
NGPs	Next-generation probiotics
NMN	Nicotinamide mononucleotide
OMVs	Outer membrane vesicles
SCFAs	Short-chain fatty acids
TLR	Toll-like receptor
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide
TNF α	Tumor necrosis factor alpha
Uro B	Urolithin B

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

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The authors declare no competing interests.

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