REVIEW

# Inflammaging and microbiota: the intersection of aging, inflammation, and gut health

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## Abstract

Inflammaging, characterized by chronic, low-grade inflammation associated with aging, is a key contributor to age-related diseases, including cardiovascular disorders, neurodegenerative conditions, and metabolic syndromes. The intricate interplay between inflammaging and the human microbiota—a diverse ecosystem of microorganisms regulating immune, metabolic, and neurological functions—is crucial in understanding these processes. Aging leads to significant shifts in microbiota composition, resulting in dysbiosis, which fosters pro-inflammatory states and systemic inflammation. Age-related changes in the gut microbiota and microbial metabolites, such as short-chain fatty acids and secondary bile acids, influence inflammation through pathways like Toll-like receptor signaling and cytokine production. Microbial dysbiosis impacts immune responses and gut barrier integrity, contributing to inflammaging and its associated pathologies. Interventions targeting gut health, including dietary modifications, probiotics, prebiotics, and fecal microbiota transplantation, offer potential strategies to mitigate these effects. Advances in bioinformatics and microbiota research enable the development of targeted treatments aimed at improving longevity and reducing chronic inflammation. Intestinal epithelial cells play a central role as physical and antimicrobial barriers, while also mediating microbiota-host immune signaling. Aging-related changes to intestinal epithelial cells, microbiota composition, and immune function disrupt immune homeostasis and exacerbate inflammaging. Environmental factors, including diet and medications, further influence gut microbiota and immune function, either preventing or promoting inflammaging. Lifestyle and pharmacological interventions are suggested to promote healthy aging and reduce the adverse effects of chronic inflammation.

**Keywords:** Aging, inflammation, dysbiosis, fecal microbiota transplantation

## Introduction

Aging is a complex, multifactorial process marked by the progressive deterioration of physiological functions [1].

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One of the hallmarks of aging is the body's increasing inability to maintain homeostasis, particularly in immune system regulation [2, 3]. Inflammaging, the chronic, low-grade inflammation associated with aging, has emerged as a crucial mechanism underlying age-related pathologies, including cardiovascular disease, cancer, and neurodegenerative disorders [4-6]. While the exact causes are not fully understood, it is believed that a combination of immunosenescence (the decline in immune function with age), cellular senescence (the process by which cells lose the ability to divide), and environmental factors (such as diet and lifestyle) play significant roles [7]. Chronic low-grade inflammation, often referred to as "inflammaging," plays a critical role in the aging process. While acute inflam-

mation is essential for tissue repair and immune function, its persistent, dysregulated state accelerates aging and exacerbates the onset of age-related diseases. This paradoxical relationship arises from the sustained activation of immune cells such as macrophages and neutrophils, which secrete pro-inflammatory cytokines that contribute to systemic tissue damage [8, 9].

Inflammaging is characterized by elevated levels of inflammatory biomarkers such as cytokines (*e.g.*, IL-6, IL-1β), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α), which are associated with frailty, cognitive decline, and mortality [10]. Unlike acute inflammation, which serves as a protective response to injury or infection, chronic inflammation contributes to tissue damage, impaired organ function, and susceptibility to disease [11]. A combination of immunosenescence (the decline in immune function with age), cellular senescence (the process by which cells lose the ability to divide), and environ-



**Figure 1. Gut dysbiosis and inflammaging**. Aging, along with multiple factors—including environmental influences, dietary changes, oxidative stress, infections, and genetic susceptibility—contributes to gut microbiota dysbiosis. This dysbiosis is characterized by a reduction in beneficial bacteria and an overgrowth of pathobionts, leading to decreased bioavailability of microbial metabolites with immunoregulatory properties, such as short-chain fatty acids (SCFAs) and secondary bile acids, thereby exacerbating gut barrier dysfunction. Increased intestinal permeability results in elevated systemic levels of lipopolysaccharides (LPS), which activate Toll-like receptor 4 (TLR4) and drive nuclear factor kappa B (NF-κB)-mediated chronic inflammation. These alterations contribute to an increased risk of neurodegenerative disorders, cardiovascular diseases (CVD), and non-alcoholic fatty liver disease (NAFLD). Created by author using assets from http://www.freepik.com/.

mental factors such as diet and lifestyle contribute to this persistent inflammatory state [12].

The gut microbiota—a vast and dynamic community of microorganisms residing in the gastrointestinal tract—plays a pivotal role in maintaining immune homeostasis and modulating systemic inflammation. Age-associated changes in microbiota composition, such as reduced diversity, decreased beneficial species, and an increased prevalence of pro-inflammatory microorganisms, lead to dysbiosis. This imbalance is implicated in the exacerbation of inflammaging through mechanisms like increased gut permeability, translocation of microbial products, and alterations in bioactive metabolites, such as short-chain fatty acids (SCFAs) [12] as shown in Figure 1.

Age-related immune dysregulation further compounds the issue, as the immune system undergoes characteristic changes with advancing age. Inflammaging fosters susceptibility to metabolic, cardiovascular, and neurodegenerative diseases, while immunosenescence impairs the immune system's ability to respond to antigens, reducing vaccine efficacy and increasing infection risk. These alterations, including reduced B cell diversity, thymic involution, and dysfunctional innate immune responses, highlight the multifaceted impact of aging on immune function [7, 12].

In addition to its biomedical implications, aging and its associated inflammatory states have significant societal consequences. The elderly, despite their wealth of knowledge and generational insights, often face social isolation and ageism, recognized as a global challenge by the WHO. Ageism is linked to worsened physical and mental health, increased loneliness, financial insecurity, and even premature death. Addressing the intersection of biological and societal factors is crucial for achieving "healthy aging," encompassing both a disease-free lifespan and enhanced quality of life through societal integration [13].

This article aims to elucidate the intricate relationship between inflammaging and gut microbiota, focusing on their roles in age-related diseases. Additionally, it explores potential interventions targeting microbiota to mitigate chronic inflammation and enhance both the healthspan and societal integration of aging individuals.

## Overview of inflammaging

Key features of inflammaging include elevated pro-inflammatory cytokines like IL-6 and TNF-α, oxidative stress driven by the accumulation of reactive oxygen species (ROS), and immune dysregulation marked by declining adaptive immunity and heightened innate immune activation [10]. Cellular senescence also plays a pivotal role, as senescent cells adopt a pro-inflammatory phenotype known as the senescence-associated secretory phenotype (SASP), which perpetuates tissue dysfunction [14].

### Interconnected sources of inflammaging

Inflammaging results from a complex interplay of various biological processes. One key factor is the presence of se-
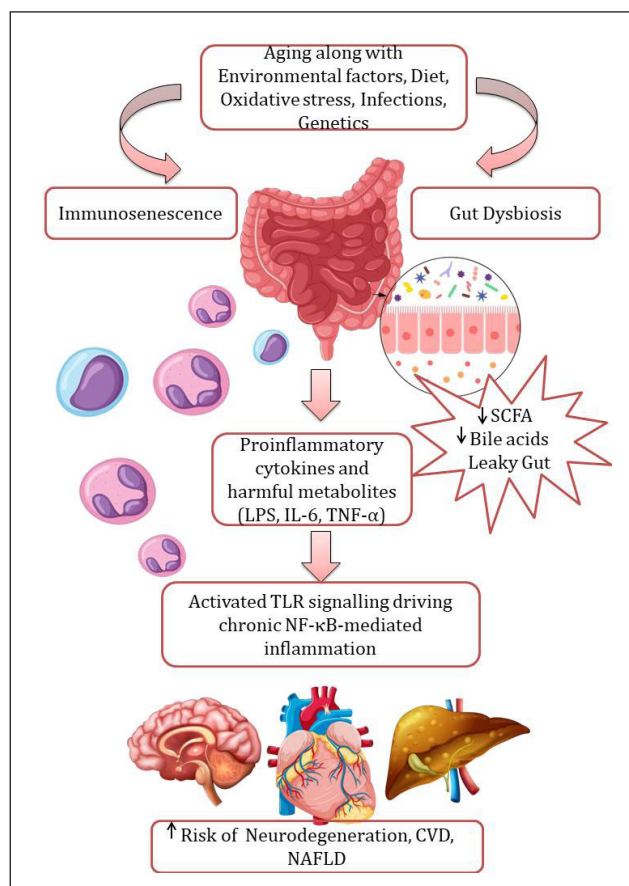
nescent cells, which secrete inflammatory cytokines, chemokines, and proteases, thereby creating a pro-inflammatory tissue environment [14]. Another contributing factor is oxidative stress, where mitochondrial dysfunction leads to the overproduction of reactive oxygen species (ROS), promoting cellular damage and triggering inflammation [2]. Age-related changes in the gut microbiota also play a role in inflammaging, as dysbiosis increases microbial translocation, which introduces lipopolysaccharides (LPS) into the circulation, thereby activating inflammatory pathways [15]. Additionally, immune system dysfunction contributes to inflammaging through immunosenescence, the decline in adaptive immune responses, coupled with heightened activation of the innate immune system, both of which foster chronic inflammation [14]. Finally, circulating mitochondrial DNA (cmtDNA) and damage-associated molecular patterns (DAMPs) act as inflammatory triggers, further exacerbating the inflammatory response [16]. Non-inflammatory contributors such as epigenetic modifications (*e.g.*, DNA methylation, histone alterations) and molecular regulators like microRNAs and altered glycosylation patterns also amplify inflammatory pathways [17]. These interconnected mechanisms establish a self-sustaining loop of chronic inflammation, underscoring the role of inflammaging in driving age-associated dysfunction and disease.

### Gut microbiota and aging

During early childhood, the diversity of the gut microbiota is characterized by the predominance of species such as *Akkermansia muciniphila*, *Bacteroides*, *Veillonella*, *Clostridium coccoides*, and *Clostridium botulinum*. By around the age of three, the gut microbiota stabilizes into a composition similar to that of adults, dominated by three primary phyla: Firmicutes, *Bacteroidetes*, and *Actinobacteria* [18]. As individuals age, changes in diet and the immune system can significantly influence gut microbiota composition. In older adults, there is often a decline in *Bifidobacterium* and an increase in *Clostridium* and *Proteobacteria*. The reduction in *Bifidobacterium*, an anaerobic bacterium known for its role in immune system stimulation, is associated with heightened inflammation and a decline in overall gut health [19].

The human microbiota, a diverse community of microorganisms residing in and on our body, plays an indispensable role in maintaining health. It influences a variety of physiological functions, including metabolic regulation, immune modulation, and barrier integrity. The gut microbiota produces SCFAs through the fermentation of dietary fibers, which in turn regulate key metabolic pathways, insulin sensitivity, and lipid metabolism. Among these, butyrate serves as a primary energy source for the colonic lining and exhibits potent anti-inflammatory and anticancer effects, contributing to overall gut and systemic health [20].

The gut microbiota also plays a crucial role in shaping adaptive immune responses, particularly in the development and differentiation of CD4$^+$ and CD8$^+$ T cells. For instance, *Lactobacillus* species stimulate and activate regulatory T cells (Tregs), while *Clostridium perfringens* (Gram-positive) supports the proliferation and differentiation of both Tregs and Th17 cells. This interaction promotes the production of interleukin-17 (IL-17) by intestinal Th17 cells, highlighting the microbiota's influence on immune modulation [21].

## Mechanisms linking microbiota and inflammaging

Inflammaging, is a hallmark of aging and is influenced by the gut microbiota. The activation of Toll-like receptors (TLRs), particularly TLR4, is a key player in this process. TLRs are type 1 transmembrane proteins found on epithelial and lamina propria cells, playing a pivotal role in the innate immune system. These receptors enable host cells to identify and respond to microbial pathogens by recognizing a diverse array of pathogen-associated molecular patterns (PAMPs) and DAMP [22].

In humans, ten TLRs have been identified, categorized based on their cellular localization. TLRs 1, 2, 4, 5, 6, and 10 are positioned on the cell surface and are primarily responsible for detecting extracellular pathogens. In contrast, TLRs 3, 7, 8, and 9 are intracellularly located, where they specialize in recognizing viral particles and other nucleic acid-based signatures. This division underscores the specialized roles of TLRs in mounting effective immune responses against diverse microbial threats [23].

TLR signaling pathways are categorized into two types: MyD88-dependent and MyD88-independent (TRIF-mediated) pathways. All TLRs, except for TLR3, utilize the MyD88-dependent pathway. TLR3 exclusively signals via the TRIF pathway, while TLR4 uniquely employs both MyD88 and TRIF pathways. Upon activation, TLRs recruit adaptor proteins such as MyD88, initiating downstream signaling cascades. This leads to the activation of transcription factors like nuclear factor-kappaB (NF-κB), interferon regulatory factors (IRF3 and IRF7), and mitogen-activated protein kinases (MAPKs). These factors drive the production of inflammatory cytokines, facilitating inflammation, immune regulation, cell survival, proliferation, and even cancer development. TLR4 exemplifies this dual pathway mechanism, engaging both TRIF and MyD88 adaptors to orchestrate a comprehensive immune response [24].

These signaling cascades underscore the complexity of TLR-mediated immune responses, linking innate immunity to broader physiological and pathological processes. TLR4 receptors recognize bacterial components like lipopolysaccharides (LPS), and when the gut barrier is compromised due to dysbiosis, these microbial products can enter the bloodstream, triggering systemic inflammation [25] as shown in Table 1.

LPS, a major component of Gram-negative bacterial cell walls, serve as potent inducers of inflammatory responses. Acting through TLRs and the NF-κB signaling pathway, LPS triggers the production of inflammatory mediators and activates the innate immune system [26]. The gut

microbiota is a primary source of LPS. Under normal circumstances, a functional intestinal barrier prevents harm by maintaining low circulating levels of LPS, as observed in healthy individuals [27, 28].

However, in pathological conditions, the intestinal barrier may lose its integrity, leading to increased permeability and heightened translocation of LPS produced by gut bacteria into the bloodstream. Historically, a leaky gut was thought to arise solely as a consequence of specific diseases. Recent studies, however, suggest that increased intestinal permeability may play a causative role in the development of certain pathological conditions, rather than being merely a secondary effect [29]. This paradigm shift highlights the importance of intestinal barrier integrity in maintaining systemic health.

Elevated levels of circulating LPS and pro-inflammatory cytokines (such as IL-6 and TNF-α) serve as biomarkers for inflammaging. Monitoring these biomarkers can help clinicians evaluate the inflammatory status of elderly patients and guide interventions, such as the use of omega-3 fatty acids or curcumin, which have anti-inflammatory properties. Restoring gut barrier integrity through dietary interventions or probiotics (*e.g.*, *Lactobacillus plantarum* or *Akkermansia muciniphila*) may help reduce systemic inflammation in aging populations [30].

Increasing SCFA production through dietary fiber supplementation or the use of specific probiotics is being studied as a clinical strategy to reduce chronic inflammation. High-fiber diets and SCFA-producing probiotics have demonstrated benefits in treating inflammatory conditions like ulcerative colitis, in experimental model [31]. Abdin AA *et al.* evaluated *Lactobacillus acidophilus* in an oxazolone-induced colitis model in rats. Results showed significant reductions in inflammatory markers (CRP, TNF-α, IL-6) and disease activity index (DAI) with *L. acidophilus* alone or combined with olsalazine, with the combination proving most effective [31]. These findings suggest *L. acidophilus* as a promising adjunct therapy for UC, warranting further clinical validation in humans. Interventions that enhance SCFA production, such as the use of butyrate-producing bacterial strains or dietary fibers, may help restore gut barrier function and reduce microbial translocation, further reducing systemic inflammation [32]. Probiotics like *Akkermansia muciniphila*, which enhance mucosal barrier function, are being evaluated for their potential to prevent gut barrier dysfunction, reduce microbial translocation, and lower systemic inflammation in the elderly [33]. Experimental studies have shown that *Akkermansia muciniphila* treatment alleviates mucosal inflammation by enhancing gut barrier function, reducing inflammatory cytokines, and improving microbial community balance [34, 35]. These findings highlight *A. muciniphila* as a promising probiotic candidate for managing colitis.

## Gut dysbiosis and its role in age-associated diseases

Gut dysbiosis, the imbalance of the gut microbiota, is a contributing factor in age-related diseases such as metabolic syndrome, cardiovascular diseases, and cancer [36]. Elderly individuals often show a reduction in beneficial bacteria like *Bifidobacteria* and *Lactobacilli*, while harm-

**Table 1.** Overview of TLR activation, signaling pathways, and gut modulation in inflammaging.

| | |
|---|---|
| **1. TLR activation and localization** | |
| Surface TLRs (*e.g.*, TLR4, TLR5) | Detect extracellular microbial components, such as LPS from gram-negative bacteria. |
| Intracellular TLRs (*e.g.*, TLR3, TLR7) | Recognize viral nucleic acids and intracellular microbial products. |
| **2. Key pathways in TLR signaling** | |
| a. MyD88-dependent pathway | |
| Step 1: Receptor activation | TLRs recruit MyD88 adaptor protein via Toll/IL-1 receptor (TIR) domains. MyD88 recruits TIRAP to stabilize the complex. |
| Step 2: Downstream signaling cascade | Activation of IRAK family kinases (*e.g.*, IRAK4 phosphorylates IRAK1). TRAF6 (TNF receptor-associated factor 6) is recruited and facilitates K63-linked polyubiquitination. |
| Step 3: Activation of NF-κB and MAPKs | TAK1 phosphorylates the IKK complex (IKKα, IKKβ, NEMO). IκBα degradation releases NF-κB, which translocates to the nucleus to induce cytokines (IL-6, TNF-α, IL-1β). MAPKs (ERK, JNK, p38) amplify responses. |
| b. TRIF-dependent pathway | |
| Step 1: Adaptor recruitment | For TLR4, LPS activation triggers MyD88-dependent signaling first. TRIF is later recruited via TRAM. |
| Step 2: Downstream activation | TRIF interacts with TRAF3 to activate TBK1 and IKKε, which phosphorylate IRF3. IRF3 induces Type I interferons (*e.g.*, IFN-β). TRIF also links to NF-κB activation via TRAF6. |
| **3. Gut modulation and its impact on TLR signaling** | |
| LPS | Dysbiosis increases circulating LPS, activating TLR4 and driving chronic NF-κB-mediated inflammation. |
| Role of SCFAs (*e.g.*, Butyrate) | SCFAs stabilize IκBα, inhibiting NF-κB activation. Promote Treg cell differentiation, reducing pro-inflammatory cytokines. |
| Probiotics and prebiotics | *Akkermansia muciniphila* and *Lactobacillus plantarum* improve mucosal integrity, reducing LPS translocation and systemic inflammation. Dietary fibers enhance SCFA production. |

ful bacteria like *Enterobacteriaceae* are more prevalent [36]. This phenomenon extends to various dietary components, such as non-digestible carbohydrates and dietary proteins that reach the colon. These substances can significantly influence bacterial composition and the microbial production of SCFAs alongside potentially harmful metabolites like hydrogen sulfide ($H_2S$), p-cresol, phenol, and ammonia ($NH_3$). Non-absorbed dietary iron, including iron supplements, also impacts the microbiota, while dietary phenolic compounds may serve as prebiotics [37]. The effects of dietary lipids on the gut microbiota remain poorly understood; however, animal studies have shown that high-fat diets (exceeding physiological norms) can induce gut dysbiosis.

Interestingly, research by Hildebrandt *et al.* demonstrated that rats fed a high-fat diet developed gut dysbiosis independently of their obese phenotype. Significant alterations in gut microbiota were observed following a switch to a high-fat diet, including a reduction in *Bacteroidetes* and an increase in both *Firmicutes* and *Proteobacteria*. These changes were consistent across different genotypes, regardless of the presence or absence of obesity. This suggests that the high-fat diet itself, rather than the obese state, is primarily responsible for the observed shifts in gut microbial composition [38].

Food additives, such as low-calorie sweeteners and emulsifiers, have been shown to disrupt the gut microbiota, increasing its potential virulence and contributing to metabolic disorders in both animals and humans [39]. Non-caloric artificial sweeteners (NAS) have been shown to contribute to glucose intolerance by inducing significant compositional and functional changes in the intestinal microbiota. These adverse metabolic effects driven by NAS consumption can be reversed through antibiotic treatment and are fully transferable to germ-free mice via fecal microbiota transplantation from NAS-consuming mice or microbiota anaerobically incubated with NAS. Microbial metabolic pathways altered by NAS correlates with increased host susceptibility to metabolic diseases [40]. In mice, low concentrations of commonly used emulsifiers, carboxymethylcellulose and polysorbate-80, were found to induce low-grade inflammation and metabolic syndrome, as well as exacerbate colitis in genetically predisposed hosts [41]. These effects were linked to microbiota alterations, including encroachment on the intestinal mucosa, changes in species composition, and heightened pro-inflammatory activity. Chaissang B *et al.*, using germ-free mice and fecal transplants demonstrated that these microbiota alterations were both necessary and sufficient to trigger inflammation and metabolic syndrome [41].

The gut microbiota are highly responsive to external influences, including drugs, diet, and environmental pollutants. Factors such as antibiotics, heavy metals, persistent organic pollutants, pesticides, nanomaterials, and food additives can significantly alter the composition and functionality of the gut microbial community, potentially disrupting its balance and contributing to health disorders [42].

The key factors influencing these shifts in microbial composition and diversity during aging, the mechanisms involved, and their potential impacts are depicted in Table 2.

## Cardiovascular disease

Intestinal bacteria generate various bioactive metabolites, which can be absorbed into the enterohepatic circulation and subsequently enter the systemic circulation, thereby influencing host physiology either directly or indirectly [43]. Trimethylamine N-oxide (TMAO) produced by the microbial metabolism of dietary choline and carnitine, has been linked to an increased risk of cardiovascular diseases (CVDs) like atherosclerosis, myocardial infarction, and stroke [44]. Elevated TMAO levels promote endothelial dysfunction and atherosclerotic plaque formation, contributing to the development of these conditions. TMAO is also implicated in increased all-cause mortality [45].

Dietary nutrient exposure influences host physiology through both metabolism-dependent and metabolism-independent mechanisms mediated by the gut microbiota. Metabolism-dependent pathways include: (1) microbial fermentation of dietary carbohydrates to produce SCFAs, which enhance host energy expenditure, inhibit histone deacetylase (HDAC) activity, and activate G-protein-coupled receptor (GPCR) signaling; (2) microbial conversion of primary bile acids into secondary bile acids, promoting brown adipose tissue (BAT) activation, energy expenditure, insulin sensitivity, and reduced inflammation; and (3) microbial transformation of choline and L-carnitine into trimethylamine (TMA), which the host flavin monooxygenase (FMO) system converts to TMAO, a compound linked to heightened CVD risk through altered cholesterol transport and macrophage activation [46].

Metabolism-independent effects arise from gut hyperpermeability, enabling translocation of bacterial components such as LPS and peptidoglycans into the bloodstream. These circulating microbial-derived molecules activate macrophages, contributing to impaired reverse cholesterol transport, insulin resistance, hyperlipidemia, and vascular inflammation. Together, the metabolism-dependent and independent actions of the gut microbiota form a complex endocrine network that modulates the risk of atherosclerotic CVD, including myocardial infarction, stroke, and associated mortality [46].

Recent clinical research has focused on leveraging the microbiome to assess cardiovascular risk. TMAO is emerging as a valuable biomarker that could help clinicians identify individuals at higher risk of developing CVDs [47, 48]. When combined with other markers viz., carnitine, creatinine, choline and betaine TMAO levels can aid in the early detection and prognosis of cardiovascular diseases [48]. Additionally, interventions targeting the gut microbiota, such as dietary modifications and the use of specific probiotics, have shown promise in reducing the production of TMAO and improving lipid profiles [49].

Dietary polyphenols can modulate the gut microbiota, influencing host metabolism through their interaction with microbial communities. The gut microbiota, in turn, metabolizes polyphenols into bioactive, low-molecular-

**Table 2.** Shifts in microbial composition and diversity during aging, the mechanisms involved, and their potential impacts.

| Key factor | Observations | Causes | Implications |
|---|---|---|---|
| Reduction in beneficial bacteria | Decline in *Bifidobacteria* and *Lactobacilli*. | Immunosenescence weakens microbial homeostasis. | Increased prevalence of potentially harmful bacteria like *Enterobacteriaceae*. |
| | Increase in *Enterobacteriaceae* species. | Reduced dietary fiber and prebiotic-rich food intake. | Reduced microbial diversity and beneficial metabolite production. |
| | | Decreased gut motility slows intestinal transit time, encouraging pathogen overgrowth. | |
| Impact of diet on microbial composition | Non-digestible carbohydrates foster SCFA production (butyrate, propionate, acetate). | Lack of undigested carbohydrates limits bacterial fermentation. | SCFAs improve gut barrier integrity and reduce inflammation. |
| | Undigested proteins produce harmful compounds ($H_2S$, p-cresol, phenol, $NH_3$). | Excess dietary protein leads to toxic metabolite production. | Toxic compounds contribute to inflammation and systemic toxicity. |
| | High-fat diets induce dysbiosis, reducing *Bacteroidetes* and increasing *Firmicutes*. | High dietary fat, independent of obesity, alters microbial balance. | Dysbiosis exacerbates metabolic inflammation. |
| | Phenolic compounds from fruits and teas support beneficial bacteria. | Lack of phenolic-rich diets diminishes prebiotic fermentation. | Reduced microbial support for health. |
| Food additives and gut microbiota | Iron supplements promote pathogenic bacterial growth. | Excess iron shifts microbial equilibrium. | Altered microbiota composition and inflammation. |
| | NAS consumption induces glucose intolerance by altering microbiota metabolic pathways. | Dysbiosis induced by NAS is transferable via microbial transplantation. | Metabolic disorders and systemic inflammation. |
| | Emulsifiers disrupt the mucosal barrier and promote low-grade inflammation. | Additives alter microbial composition and increase bacterial encroachment. | Exacerbated colitis, metabolic syndrome, and barrier dysfunction. |
| External influences on microbiota | Antibiotic overuse disrupts microbial diversity. | Environmental pollutants (heavy metals, pesticides) affect microbiota functionality. | Increased prevalence of opportunistic pathogens and dysbiosis. |
| | PPIs and NSAIDs alter microbial composition. | Drug-microbiota interactions reduce diversity and increase disease risk. | Heightened susceptibility to inflammation and gut-related disorders. |
| Loss of microbial diversity | Aging reduces overall microbial diversity. | Chronic inflammation alters gut environment. | Correlation with frailty, inflammation, and poor health outcomes. |
| | Decreased SCFA production reduces beneficial metabolites. | Physical inactivity decreases microbial richness. | Reduced regulatory T-cell differentiation and barrier integrity. |
| Metabolic and immune consequences | Pro-inflammatory state ("leaky gut") increases systemic inflammation. | Microbial metabolites (*e.g.*, LPS) enter circulation. | Inflammaging and age-associated diseases. |
| | Reduced SCFAs impair gut barrier function and anti-inflammatory pathways. | Loss of beneficial bacteria limits SCFA production. | Weakened gut barrier and increased infection susceptibility. |

weight phenolic compounds that contribute to the host's regulatory and metabolic pathways. These compounds play a significant role in shaping the composition and functionality of the intestinal microbiota. Polyphenols selectively promote the growth of beneficial microorganisms, such as *Lactobacillus* and *Bifidobacterium*, which have the potential to ameliorate inflammation [50].

In a study by Koeth RA *et al.* the potential of gut microbial modulation as a strategy to reduce TMAO production, thereby mitigating CVD risk was highlighted. The research revealed that individuals with a gut microbiota dominated by *Prevotella* exhibited higher circulating TMAO levels compared to those with a *Bacteroides*-enriched enterotype. Furthermore, omnivorous participants with elevated plasma TMAO concentrations had an increased abundance of *Peptostreptococcaceae* and *Clostridium* and a reduced prevalence of *Lachnospira* compared to vegan or vegetarian individuals, who demonstrated lower TMAO levels [51]. Moreover, postbiotics, which are metabolites produced by probiotics, are being explored as an innovative therapeutic strategy for modulating cardiovascular inflammation, with promising results emerging from early clinical trials [52].

## Neurodegenerative diseases: Alzheimer's and Parkinson's

Microbial dysbiosis not only contributes to systemic inflammation, but also affects the brain through the gut-brain axis. This communication pathway links the gut microbiota with the central nervous system (CNS), influencing neuroinflammation, cognitive function, and the progression of neurodegenerative diseases like Alzheimer's and Parkinson's. Alterations in gut microbiota composition can activate microglia, the brain's immune cells, contributing to neuroinflammation and cognitive decline [53]. Dysbiosis—the imbalance of the gut microbiota—along with increased gut permeability, contributes to systemic inflammation and neuroinflammation, two key drivers of neurodegenerative disease progression. This connection is further complicated by the gut-brain axis, a bidirectional communication system linking the central nervous system and the gastrointestinal tract [54].

The gut microbiota metabolize dietary elements such as macronutrients, micronutrients, fiber, and polyphenols into various bioactive compounds, including short-chain fatty acids, trimethylamines, amino acid derivatives, and vitamins. These metabolites, along with the dietary components, play critical roles in metabolic and signaling processes, influencing host homeostasis, including the integrity of the blood-brain barrier (BBB) and overall brain function [55]. SCFAs can influence brain neurotransmission by regulating the expression and functionality of neurotransmitters and their receptors. Among SCFAs, butyrate is particularly noteworthy for its significant impact on neuronal activity. It has been shown to modulate key neurotransmitters such as glutamate, the brain's primary excitatory neurotransmitter involved in synaptic plasticity and memory, and GABA, the principal inhibitory neurotransmitter that maintains the balance between neuronal excitation and inhibition [56]. Butyrate's effects on the glutamatergic system include regulating glutamate receptor expression and neurotransmitter release, thereby influencing neuronal excitability and synaptic signaling [57]. Similarly, its role in GABA-mediated transmission underscores its importance in neural stability and cognitive function.

Furthermore, butyrate inhibits HDACs, promoting histone acetylation, which relaxes chromatin structure and enhances gene transcription, including the upregulation of brain-derived neurotrophic factor (BDNF). Increased BDNF expression supports neurogenesis, the generation of new neurons from neural stem cells, and enhances synaptic plasticity [58, 59]. These processes contribute to improved learning and memory capabilities and offer promising therapeutic potential for addressing neurodegenerative disorders.

Preclinical studies have shown that gut dysbiosis can accelerate beta-amyloid deposition in the brain and worsen cognitive impairment in Alzheimer's disease (AD) [60, 61]. Guillemin GJ *et al.* explored the impact of quinolinic acid, a tryptophan-derived metabolite, on AD. The results revealed that elevated levels of quinolinic acid exacerbated neuroinflammation by increasing microglial activation and astrogliosis, hallmarks of brain inflammation [61]. This study highlights quinolinic acid as a key factor in AD progression and underscores its potential as a target for therapeutic intervention.

Probiotic treatment in mice has been shown to enhance spatial memory and reduce hippocampal plaque accumulation [62]. Supplementation also improved synaptic plasticity and restored long-term potentiation in amyloid-beta (Aβ)-treated mice [63]. Interventions targeting the gut microbiota, such as prebiotics and probiotics, may improve cognitive function and slow the progression of neurodegenerative diseases in older adults [64]. In humans, a clinical trial reported that probiotics improved cognitive function in Alzheimer's disease (AD) patients and positively influenced plasma biomarkers, including malondialdehyde and serum triglycerides [65].

Patients with Parkinson's disease (PD) often experience intestinal dysbiosis, marked by a decrease in SCFA-producing bacteria and an increase in proinflammatory microbial species [66]. This imbalance can disrupt the production of metabolites that regulate inflammation both systemically and in the brain. A reduction in butyrate levels may play a role in the chronic activation of microglia, a hallmark of PD pathology that contributes to neurodegeneration. This sustained microglial activation is thought to aggravate neuronal damage, accelerating disease progression [67].

Chang *et al.* investigated metabolic profile changes, focusing on kynurenine metabolism in the plasma of PD patients. Their findings suggest that these metabolic alterations may influence disease progression by modulating neuroinflammatory pathways [68]. Shao *et al.* highlighted advancements in metabolomics, emphasizing that pre-

clinical studies have revealed notable alterations in metabolites such as lactate and SCFAs. These metabolites are of particular interest due to their potential contribution to mitochondrial dysfunction and neuroinflammation, both key features of PD [69].

In clinical settings, therapeutic modulation of the gut-brain axis is gaining traction as a potential strategy for managing neurodegenerative diseases. Clinical trial investigating the use of probiotics supplementation containing: *Bifidobacterium bifidum*, *Lactobacillus casei*, *Lactobacillus fermentum*, and *Lactobacillus acidophilus* have shown potential in slowing cognitive decline in patients with mild cognitive impairment, a precursor to AD, suggesting that gut microbiota modulation could delay AD progression [65]. Similarly, analysis of mucosal and stool samples from individuals with PD revealed significant down-regulation of several genes in the stool microbiota, alongside substantial alterations in microbial composition. Specifically, an increase in bacteria such as *Proteobacteria*, *Betaproteobacteria*, *Coprococcus*, *Blautia*, *Akkermansia*, *Oscillospira*, *Roseburia*, and *Bacteroides* was observed. Conversely, there was a notable decrease in beneficial bacterial groups like *Faecalibacterium*, Firmicutes, and members of the class *Clostridia*. These microbial imbalances may play a role in PD pathophysiology, potentially influencing gut-brain signaling and contributing to disease progression [70].

## Metabolic disorders

The gut microbiota plays a crucial role in regulating metabolism, and dysbiosis has been implicated in several metabolic disorders, including type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and obesity [71]. One of the key mechanisms by which the microbiota influences metabolic health is through the process of metabolic endotoxemia [72]. This occurs when microbial products such as LPS translocate from the gut into the bloodstream, triggering chronic low-grade inflammation and insulin resistance.

In clinical practice, microbiota-based therapies are being explored as adjuncts to conventional treatments for metabolic disorders. Several studies explored multi-strain probiotic formulations, such as Sabico *et al*, which showed significant improvements in HOMA-IR after 6 months of probiotic supplementation [73]. Other studies, such as Mafi *et al*., who utilized *Lactobacillus*, *Bifidobacterium* and *Streptococcus* and, Razmpoosh *et al*., using *Lactobacillus* with *Bifidobacterium* reported improvements in cardiometabolic risk factors and fasting plasma glucose [74, 75]. Perraudeau *et al*., noted that a five-strain probiotic formulation reduced postprandial glucose levels but did not significantly affect weight or HOMA-IR [76]. Jiang *et al*., found that probiotic supplementation improved glycemic control in T2DM patients with diabetic nephropathy, underlining the potential of probiotics in managing diabetes-related complications [77]. In another study, Toejing *et al*., found that *Lactobacillus paracasei* HII01 supplementation reduced inflammatory markers and hyperglycemia, potentially by modulating the gut microbiota and treating endotoxemia, which suggests a promising role as an adjunctive therapy [78]. Kumar *et al*., explored the impact of probiotics as an adjunct therapy to metformin, finding reductions in fasting blood glucose (FBG), postprandial glucose, and HbA1c levels compared to metformin alone, although the overall efficacy of probiotics in this combination treatment was not strongly substantiated [79].

Other studies also assessed the effects of different probiotic strains, with varying results. Chen *et al*., reported that the combination of metformin with a blend of multiple probiotics resulted in a more pronounced hypoglycemic effect, likely through modulation of the gut microbiota and bile acid metabolism [80]. Hasanpour *et al*. highlighted that a combination of soymilk and probiotics improved cardiovascular risk factors in T2DM patients, though no significant effects were observed on FBG or HOMA-IR [81].

## Microbiota modulation as a strategy to combat inflammaging

The gut microbiota represents a promising therapeutic target for mitigating inflammaging, as its composition and functionality profoundly influence host immune responses and metabolic health. Several microbiota modulation strategies, including dietary interventions, probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT), have been explored for their potential to combat inflammaging. Below, we discuss these strategies and their underlying mechanisms.

### Dietary interventions

Dietary fibers, primarily composed of non-digestible carbohydrates, significantly influence the gut microbiota by serving as substrates for microbial fermentation. The molecular mechanisms underlying the beneficial effects of high-fiber diets on gut microbiota composition and systemic inflammation involve several interconnected pathways [82, 83].

Dietary fiber, though resistant to digestion in the upper gastrointestinal tract, undergoes fermentation in the colon by specific bacterial taxa, such as *Bifidobacterium* and *Lactobacillus* species. These microbes possess specialized enzymes, including glycoside hydrolases and polysaccharide lyases, which break down complex carbohydrates into fermentable monosaccharides. This process yields SCFAs, including acetate, propionate, and butyrate, which play pivotal roles in maintaining gut health and modulating inflammation. These commensal microbes compete with pathogenic species through mechanisms like antimicrobial peptide production and acidification of the colonic environment via lactic acid and SCFA production [84].

The immune system also benefits significantly from fiber-rich diets. SCFA-mediated signaling suppresses systemic inflammation by reducing the levels of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis

factor-alpha (TNF-α). These effects are achieved through inhibition of inflammatory transcription factors such as NF-κB in immune cells. SCFAs also serve as epigenetic regulators, modulating histone acetylation and methylation patterns to influence the transcription of genes involved in inflammatory responses [46, 58]. High-fiber diets affect microbial tryptophan metabolism, leading to the production of indole derivatives that activate the aryl hydrocarbon receptor (AhR). This receptor plays a crucial role in modulating intestinal immunity and inflammation, highlighting the broader implications of fiber fermentation in systemic health [85].

Enhanced microbial production of butyrate has also been linked to improved insulin sensitivity and lipid metabolism, highlighting its potential in mitigating systemic metabolic dysfunction [80]. These interconnected mechanisms underscore the critical role of dietary fiber and its fermentation products in maintaining overall health and preventing disease.

### Probiotics

Probiotic supplementation, particularly with specific strains such as *Lactobacillus rhamnosus*, *Lactobacillus casei*, and *Bifidobacterium longum*, has gained prominence as a therapeutic strategy for modulating gut microbiota composition and alleviating inflammation in aging populations. These effects are mediated through intricate molecular mechanisms involving immune modulation, enhancement of the intestinal barrier, and alterations in microbial metabolite production.

### Immune modulation by probiotic strains

Probiotic strains play a critical role in modulating the immune system by interacting with the gut-associated lymphoid tissue (GALT) and influencing both innate and adaptive immune responses. This interaction is mediated through specific molecular pathways, including pattern recognition receptors (PRRs). Probiotics, such as *Lactobacillus rhamnosus*, engage TLRs and NOD-like receptors (NLRs) on intestinal epithelial and immune cells [86]. For instance, binding to TLR-2 triggers MyD88-dependent NF-κB signaling pathways, resulting in the controlled production of anti-inflammatory cytokines like IL-10, while suppressing pro-inflammatory cytokines such as IL-6 and TNF-α. Additionally, probiotics influence dendritic cells by inducing tolerogenic phenotypes, which, in turn, promote the differentiation of Tregs. Tregs contribute to immune homeostasis by secreting anti-inflammatory mediators, including IL-10 and TGF-β, thereby reducing chronic inflammation, a hallmark of aging [86].

### Enhancement of intestinal barrier function

Probiotic strains also strengthen the integrity of the intestinal barrier, which tends to weaken with age, leading to increased systemic inflammation [87]. One mechanism involves the upregulation of tight junction proteins, such as occludin, claudin, and zonula occludens-1 (ZO-1) [84]. For example, *Bifidobacterium longum* enhances ZO-1 expression via the PI3K/Akt signaling pathway, thereby decreasing epithelial permeability and preventing the translocation of endotoxins [88]. Furthermore, probiotics stimulate goblet cells to increase mucin production, particularly MUC2, which enhances the protective mucus layer on the epithelial surface and limits microbial invasion. By fortifying the gut barrier, probiotics reduce endotoxemia by minimizing lipopolysaccharide (LPS) translocation, which otherwise triggers systemic inflammation through TLR-4 signaling [84].

### Microbial metabolite modulation

Probiotics contribute to the production of beneficial microbial metabolites with anti-inflammatory properties. Notably, they enhance the generation of SCFAs such as acetate, propionate, and butyrate by fostering the growth of SCFA-producing bacteria. These SCFAs act as ligands for G-protein-coupled receptors, including GPR43 and GPR109A, which inhibit NF-κB signaling and suppress the release of pro-inflammatory cytokines [46, 58, 59]. Additionally, probiotics influence tryptophan metabolism, leading to the formation of indole derivatives that activate the aryl hydrocarbon receptor (AhR) pathway. This activation supports mucosal homeostasis and reduces inflam-

**Table 3.** The synergistic mechanism of action and outcomes of synbiotics.

| Mechanism | Key actions | Outcomes |
| --- | --- | --- |
| Enhanced growth and activity of beneficial bacteria | • Prebiotics (inulin, FOS, GOS) selectively fuel probiotic strains like *Lactobacillus* and *Bifidobacterium*.<br>• Amplifies metabolic activity of probiotics, increasing SCFA production. | Impaired protein folding, decreased chaperone function (HSP70, HSP90), and defective autophagy. |
| Improved gut barrier integrity | • Probiotics secrete antimicrobial peptides and regulate tight junction proteins (*e.g.*, occludin, claudin).<br>• Prebiotics enhance the mucus layer by stimulating goblet cells for mucin production. | Decreased chaperone activity, proteasome dysfunction and reduced autophagic activity. |
| Anti-inflammatory effects | • Downregulates NF-κB signaling, reducing pro-inflammatory cytokines (*e.g.*, TNF-α, IL-6).<br>• SCFAs act as HDAC inhibitors, promoting anti-inflammatory epigenetic changes. | Impaired protein quality control (UPS and autophagy), reduced mitochondrial function, and accumulation of protein aggregates. |
| Modulation of metabolic pathways | • Enhances insulin sensitivity and lipid metabolism via SCFA-mediated GPR activation.<br>• Reduces endotoxemia and LPS-induced inflammation by improving gut permeability. | Improves glycemic control, lipid profiles, and metabolic health. |

mation [85].

## Prebiotics

Prebiotics, such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), are non-digestible food components that selectively stimulate the growth and activity of beneficial gut microbiota, including *Bifidobacterium* and *Lactobacillus* species. Their fermentation in the colon yields metabolites like SCFAs, which exert both local and systemic effects that contribute to anti-inflammatory and metabolic benefits. These mechanisms make prebiotics a promising intervention for addressing dysbiosis and chronic low-grade inflammation associated with aging, known as inflammaging [84].

## Synbiotics

Synbiotics combine prebiotics and probiotics to provide synergistic benefits. This approach not only stimulates the growth of beneficial bacteria but also enhances their activity and survival in the gastrointestinal tract. Synbiotics also exhibit potential in reducing gut permeability, a hallmark of chronic inflammation associated with aging [84, 89]. The synergistic mechanism of action and outcomes of synbiotics is shown in Table 3.

## Fecal microbiota transplantation (FMT)

FMT is an innovative therapeutic approach involving the transfer of stool from a healthy donor to a recipient to restore microbial diversity and functionality in the gut. This method, initially established for its efficacy in treating *Clostridioides difficile* infections, is now gaining traction as a potential intervention to mitigate inflammaging [89]. In the context of aging, where dysbiosis is often driven by dietary alterations, medication use, and age-related physiological changes, FMT offers a promising avenue for re-establishing microbial homeostasis and alleviating its downstream effects on health.

The primary mechanism underlying the benefits of FMT lies in its ability to restore microbial diversity. Aging is frequently accompanied by a decline in beneficial gut microbial populations, such as *Bifidobacterium* and *Faecalibacterium*, coupled with an overgrowth of pro-inflammatory species. The reintroduction of a balanced microbial community through FMT promotes ecological stability and re-establishes a functional microbiota capable of supporting host health. This restoration is particularly crucial in aging populations, where microbial diversity is a determinant of gut and systemic health [89].

Another critical benefit of FMT is its ability to enhance gut barrier integrity. The introduction of beneficial bacteria through FMT stimulates the production of SCFAs, such as butyrate, which strengthen intestinal tight junctions and enhance mucus production. Improved gut barrier function reduces intestinal permeability, a phenomenon that often leads to endotoxin translocation and systemic inflammation in aging populations. By reinforcing gut barrier integrity, FMT helps mitigate the cycle of dysbiosis, inflammation, and metabolic disruption [90].

By reinstating beneficial bacteria, FMT suppresses the overgrowth of pathogenic microbes that release inflammatory triggers like LPS. These transferred microbes modulate inflammatory pathways, particularly by downregulating NF-κB signaling, thereby reducing the production of pro-inflammatory cytokines such as TNF-α and IL-6. The resulting anti-inflammatory effects are crucial for mitigating chronic low-grade inflammation that contributes to age-associated diseases [89, 91].

Moreover, FMT has shown promise in modulating the gut-liver axis, a critical interface affected by dysbiosis in aging. Dysbiosis disrupts bile acid metabolism, exacerbating systemic inflammation and metabolic disturbances. FMT restores the balance of bile acid-metabolizing bacteria, thereby regulating bile acid signaling pathways involved in lipid metabolism and inflammatory responses. This modulation of the gut-liver axis is particularly relevant for addressing metabolic disorders commonly associated with aging [91].

Emerging evidence also suggests that FMT has beneficial effects on the gut-brain axis, which is intricately linked to aging and neuroinflammation. Dysbiosis in the elderly has been associated with cognitive decline and neurodegenerative diseases such as Alzheimer's and Parkinson's. By influencing microbial composition and reducing systemic inflammation, FMT may help mitigate neuroinflammation and improve cognitive outcomes in these populations [89]. FMT represents a promising therapeutic strategy to address the systemic inflammation, metabolic disturbances, and cognitive decline associated with aging. While existing evidence is encouraging, further research is essential to refine treatment protocols, optimize donor selection, and ensure long-term safety and efficacy. These advancements could pave the way for the broader application of FMT in addressing the challenges posed by inflammaging.

## Conclusions

The relationship between microbiota and inflammaging is a rapidly evolving field with significant clinical implications. Microbiota-targeted interventions could reduce inflammation, improve metabolic health, and promote longevity. Integrating microbiome profiling into clinical practice will enable personalized treatments that address the underlying causes of inflammaging and related diseases. The convergence of microbiota science and aging research holds promise for enhancing immune function and reducing chronic disease burdens in older adults. Aging is often associated with microbial dysbiosis, linked to diseases like obesity, metabolic syndrome, cardiovascular disease, and neurodegeneration. Dysbiosis contributes to metabolic disturbances, insulin resistance, and cardiovascular risk through inflammation and harmful microbial metabolites such as TMAO. Restoring microbial balance through diet or probiotics shows promise in improving metabolic health and reducing cardiovascular risk. Furthermore, therapies like FMT are being explored for neurodegenerative diseases, aiming to restore microbial balance, reduce

neuroinflammation, and slow disease progression in aging individuals.

## Declarations

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