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REVIEW ARTICLE

The microbiota–epigenome axis in healthy longevity: roles of microbial and gerobiotic metabolites — a narrative exploratory review

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Abstract Aging is a dysbiotic and pro-inflammatory process that increases susceptibility to multiple chronic comorbidities. Centenarians and supercentenarians offer a unique biological model for elucidating the molecular determinants of healthy aging and exceptional longevity, as they display distinctive epigenetic signatures and a gut microbiome configuration that diverges from both younger and typically aging individuals, although substantial interindividual variability exists. The gut microbiota constitutes a strategic hub of microorganisms and bioactive metabolites with probiotic and postbiotic potential that modulate host epigenetic circuits through precursors and substrates for epigenetic "writer" and "eraser" enzymes, thereby shaping the aging trajectory. In this review, we examine the interactions between the microbiota and its metabolites, including short-chain fatty acids, lipopolysaccharides, trimethylamine N-oxide (TMAO), p-cresol, and secondary bile acids, and their roles in epigenetic modulation associated with healthy aging. We highlight (i) the attenuation of classical pro-inflammatory pathways through downregulation of NF-κB/COX-2, modulation of the Th17/Treg balance, and also the lower systemic LPS levels of centenarians, which are associated with enhanced SIRT1 activity (↑LPS/↓SIRT1); (ii) the reprogramming of energy metabolism via activation of SIRT1/AMPK and SIRT1/p-53, modulation of mTOR, and attenuation of the IGF-1/insulin axis; (iii) the strengthening of the intestinal barrier through upregulation of tight junction proteins such as ZO-1, occludin, and claudins, resulting in reduced permeability and zonulin levels; and (iv) the optimization of antioxidant defenses. Collectively, these findings suggest translational potential for microbiota-derived metabolites in gerobiotic strategies, although clinical evidence remains limited.

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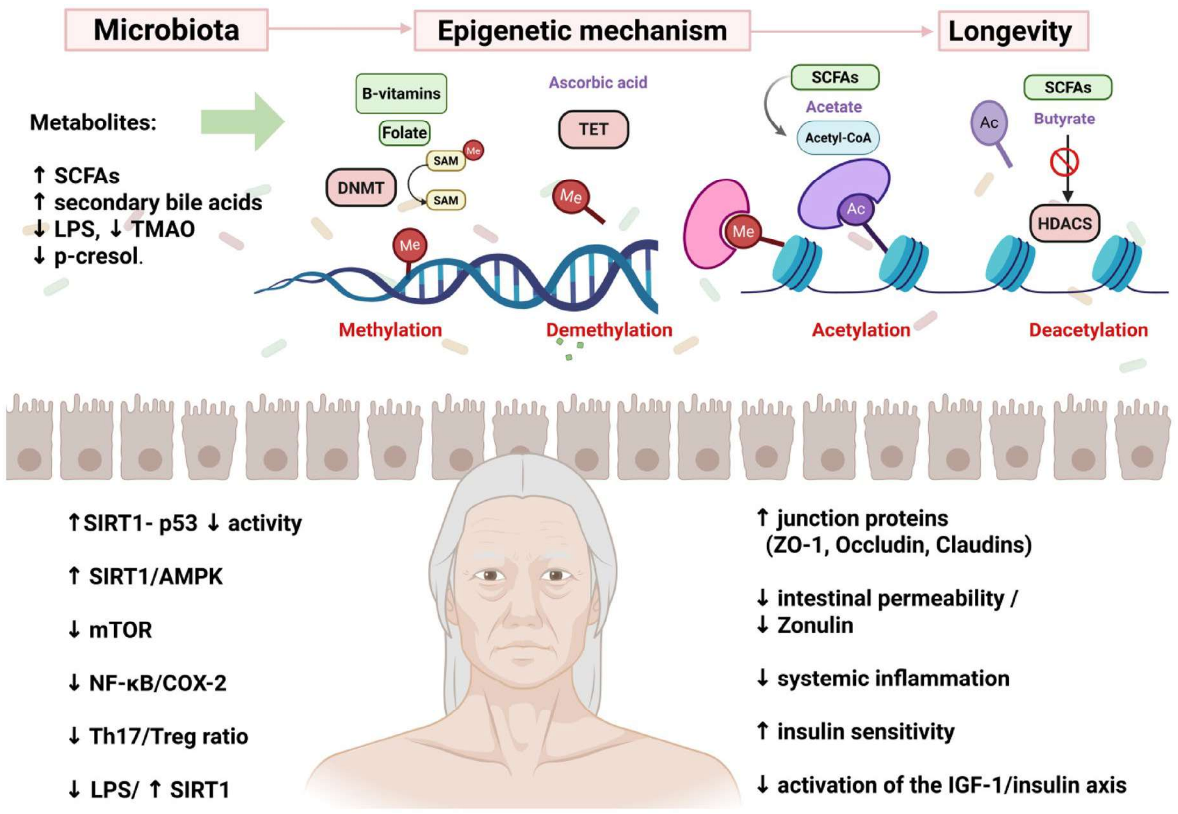
Graphical Abstract



Keywords Epigenetic regulation · Short-chain fatty acids · Secondary bile acids · Sirtuins · HDAC · Gerobiotics

Introduction

Healthy aging and longevity have become pivotal focal points in contemporary biomedical research, particularly considering global demographic projections indicating that the population aged 60 years and older will surpass two billion individuals by 2050 (World Health Organization 2024). This demographic shift is likely to be accompanied by a significant rise in comorbidities associated with aging, including neurological disorders and metabolic syndromes, which pose considerable challenges to health systems and the economy. It is important to note, however, that the chronological age does not always align with the biological age. Individuals who attain exceptional longevity often exhibit a biological age that is younger than their chronological age, as evidenced by findings from epigenetic clocks and DNA methylation analyses (Daunay et al. 2022).

The Blue Zones of Longevity are geographically isolated regions, including islands and mountainous areas, recognized as focal points for exceptional longevity. These regions exhibit a higher proportion of centenarians relative to their total population compared to other areas worldwide. They serve as natural laboratories for identifying patterns associated with healthy aging, encompassing lifestyle habits, genetic traits, epigenetic factors, and intestinal microbiota (Ulusu 2024; Mishra 2009). While it is understood that microbiota undergoes changes throughout the aging process, centenarians possess a microbiota characterized by antioxidant properties and protective effects against various pathologies. However, it is still poorly understood how the intestinal microbiota modulates the epigenetic marks and what are the key species and bacterial consortia associated with the epigenetic process of longevity. Therefore, it is worth emphasizing that we took centenarians from longevity zones as heuristic models rather than as definitive causal evidence of longevity, while acknowledging both the strengths of Blue Zone populations as natural experimental models and the controversies related to demographic validation and methodological limitations.

The history of probiotics is marked by the observation of Nobel laureate Elie Metchnikoff, who associated the longevity of Bulgarian farmers with the consumption of probiotic yogurt containing *Bacillus bulgaricus* (Idrees et al. 2022). The activity of the microbiota and its interaction with the host corresponds to a metaorganism, whose symbiotic association is critical for the process of health and disease. Microbiota metabolite production influence epigenetic active substances that regulate the cellular transcriptional response. This occurs through the modulation of noncoding RNAs (ncRNAs) and enzymes that include or erase histone posttranslational modifications, methylate or erase methyl groups from DNA, remodel chromatin, include histone variants and other epigenetic processes (Woo & Alenghat 2022). In this scenario, probiotics stand out as a modulating intervention of the intestinal microbiota that may modify cellular epigenomes, favoring the prevention and mitigation of diseases, as well as increasing life prospects.

In this exploratory study, we investigated the influence of the intestinal microbiota compositionon key epigenetic pathways that regulate metabolic and immunological homeostasis in centenarians hosts. By integrating data from the microbiota and its metabolites, we aim to identify epigenetic signatures linked to longevity and provide evidence that supports the formulation of preventive and therapeutic strategies designed to promote healthy aging through the application of probiotics and gerobiotics.

Methodology

An exploratory narrative review was conducted using PubMed, Scopus, and Web of Science databases, with searches performed between November 2023 and July 2025. Meta-analyses, systematic reviews, and controlled clinical trials published in the last ten years (2015–2025) were considered for analysis, provided they addressed centenarians and supercentenarians, the aging process in Blue Zones and other regions characterized by a high prevalence of longevity, as well as the interface between epigenetics and the microbiota associated with longevity. The initial screening step was based on reading titles and abstracts, with the aim of excluding records outside the defined scope. The eligible articles were subsequently analyzed in full. To conduct the study, the guidelines of the *Scale for the Assessment of Narrative Review Articles* (SANRA) were adopted, which encompass fundamental criteria, including justification of the relevance of the topic, explicit definition of objectives, description of the search strategy, adequate referencing, consistency of scientific reasoning, and appropriate presentation of data (Baethge et al. 2019). The schematic images presented in this study were created using the BioRender platform (https://biorender.com).

Biomarkers and lifestyle patterns among centenarians from regions remarkable regions for longevity

Biological aging is an inevitable process of progressive decline in tissues and organs, marked by reduced protective and regenerative mechanisms and a low-grade chronic inflammatory state known as inflammaging (Choudhary et al. 2023). This phenomenon heightens the risk of age-related morbidities, such as neurodegenerative diseases, cardiovascular conditions, and cancer (Li et al. 2023). The cellular hallmarks of aging are extensively documented and encompass genomic instability, telomere attrition, mitochondrial dysfunction, failure to detect nutrients, increased oxidative stress, dysfunctional macroautophagy and changes in the intestinal microbiota (Li et al. 2023; Mahamud et al. 2025) (Fig. 1a).

As individuals age, there is a significant decline in the activity of antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR). This decline is accompanied by increased levels of oxidative stress markers, such as malondialdehyde

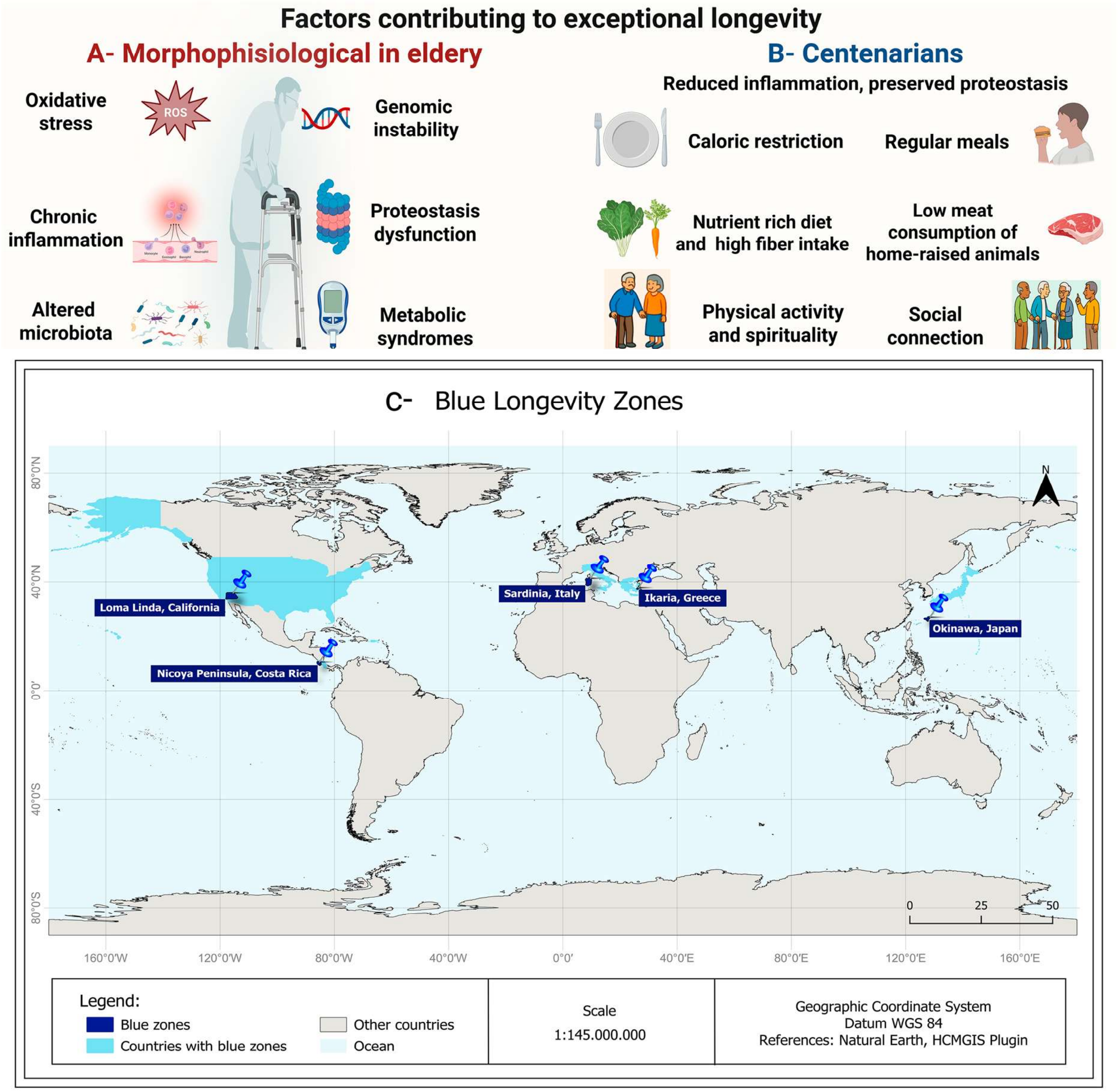


Fig. 1 Factors associated with exceptional longevity and the geographic distribution of Blue Zones **A** Common morphophysiological alterations associated with aging encompass oxidative stress, chronic inflammation, genomic instability, dysfunction in proteostasis, alterations in gut microbiota, and the presence of metabolic syndromes. **B** Centenarians display characteristics associated with healthy longevity, including caloric restriction, regular meal patterns, diets rich in fiber and low in meat, maintained proteostasis, diminished systemic inflammation, engagement in physical activity, spiritual practices, and robust social connections. **C** A world map depicting the geographic distribution of the Blue Zones—regions characterized by a high concentration of centenarians—includes Loma Linda (USA), the Nicoya Peninsula (Costa Rica), Sardinia (Italy), Ikaria (Greece), and Okinawa (Japan)

(MDA), superoxide anion ($O_2\bullet^-$), and reduced glutathione (GSH). The resulting imbalance leads to an overproduction of reactive oxygen species (ROS), which contributes to cumulative damage to both nuclear and mitochondrial DNA, impaired repair mechanisms, loss of nucleoli, increased resistance to apoptosis, and ultimately, cellular senescence (DiLoreto & Murphy 2015). Interestingly, centenarians show lower levels of lipid peroxidation and oxidized plasma proteins—particularly among women—and exhibit a unique redox profile characterized by enhanced antioxidant capacity and reduced ROS production, compared to both elderly and younger individuals from the same geographic area (Belenguer-Varea et al. 2020; Lozada-Martinez et al. 2024).

Systemic, chronic inflammation associated with aging, even in the absence of identifiable triggers, is a significant negative predictor of longevity and a hallmark of accelerated aging, as demonstrated in animal models (Arai et al. 2015; Sanada et al. 2018). Immunosenescence is characterized by increased levels of circulating pro-inflammatory cytokines, including interleukins IL-1, IL-6, tumor necrosis factor alpha (TNF-α), and interferons (Ferrucci & Fabbri 2018). Interestingly, centenarians display a distinct immunological profile, marked by a lower Th17/Treg ratio and decreased secretion of inflammatory cytokines (Zhou et al. 2022). Another intrinsic hallmark of aging is the age-related disruption of proteostasis, which involves the accumulation of misfolded proteins, impaired protein solubility, and autophagic dysfunction. However, centenarians seem to maintain protein homeostasis like that of younger adults, likely due to adaptive mechanisms such as the efficient activation of the ubiquitin–proteasome system (Frankowska et al. 2023). Furthermore, centenarians typically exhibit lower insulin resistance, improved glycemic control, and favorable triglyceride levels—factors that are associated with a reduced risk of all-cause mortality (S. Yan et al. 2025).

Beyond cellular and molecular mechanisms, environmental and lifestyle factors play a significant role in influencing longevity. The Blue Zones (BLZs) of longevity—validated population-based models that include Okinawa (Japan), Sardinia (Italy), the Nicoya Peninsula (Costa Rica), Icaria (Greece), and Loma Linda (California, USA) (Fig. 1-c)—are characterized by a high prevalence of centenarians and similar lifestyle patterns. These patterns typically feature predominantly plant-based diets, moderate caloric restriction, regular physical activity, strong social connections, and spiritual engagement (Kreouzi et al. 2024). In observacional studies, these factors have been associated with improved insulin sensitivity (Angelino et al. 2022; Kreouzi et al. 2024).

In certain regions, caloric intake is generally lower yet nutritionally dense, often characterized by moderate caloric restriction of approximately 10–15% and the cultural practice of consuming food until about 80% satiety is achieved (Kreouzi et al. 2024). These diets are abundant in vegetables, whole grains, green leafy vegetables, yellow root vegetables (such as sweet potatoes), legumes, and fruits (Nieddu et al. 2020). While meat consumption is limited, it is not entirely excluded; typically, it is sourced from locally raised animals and involves minimal exposure to ultraprocessed foods (Fig. e 1-b) (Nieddu et al. 2020). Additional factors contributing to healthy aging trajectories include frequent interactions with farm animals and the absence of sanitation infrastructure during early life (Sepp et al. 2022), as well as physically active lifestyles that encompass walking, domestic chores, and agricultural work (Martucci et al. 2017). Isolated mountainous regions, characterized by pastoral traditions and above-average levels of physical activity, exhibit similar longevity profiles (Wang et al. 2022). Moreover, most centenarians live with family members in multigenerational households, which enhances social support and access to care (Aiello et al. 2021).

Gut microbiota composition and metabolite profiles in centenarians

In this context, the gut microbiota plays a pivotal role in connecting environmental factors to the modulation of physiological mechanisms associated with healthy aging and longevity (Fang et al. 2021). It is regarded as a transducer of environmental signals, consisting of a multispecies consortium of bacteria, fungi, viruses, and bacteriophages. Commonly referred to as microbiome, the gut microbiota possesses a genetic repertoire that surpasses the size of the human genome by more than 100-fold (P. C. Lee et al. 2022). The age-related decline in microbial diversity, often associated with edentulism, reduced fiber intake, altered intestinal motility, polypharmacy, and immunosenescence—has been correlated with poorer clinical outcomes in older adults, indicating a loss of the host's genetic and metabolic repertoire (Biagi et al. 2016). In contrast, centenarians from diverse populations demonstrate enhanced gut microbial diversity, maintenance of core taxa, and an enrichment of functional groups linked to anti-inflammatory, antioxidant, and

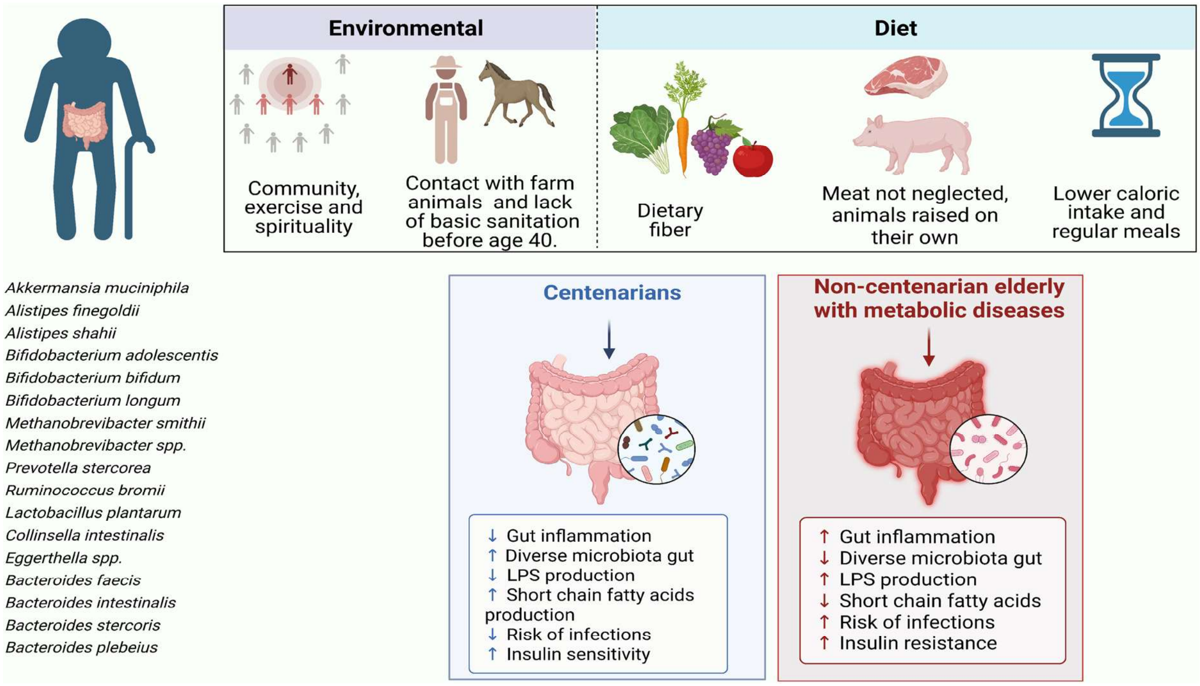


Fig. 2 Environmental factors, life habits and intestinal microbiota composition in centenarians from regions with high longevity prevalence ("Blue Zones"), compared to non-centenarian elderly individuals with metabolic diseases

metabolic advantages (Tuikhar et al. 2019; Ren et al. 2021; Sepp et al. 2022) (Fig. 2).

Despite the absence of a universally accepted taxonomic signature for the microbiota of centenarians, certain structural and functional patterns have been consistently observed. These include a notable abundance of short-chain fatty acid (SCFA)-producing species (Pang et al. 2023), xenobiotic-degrading microbes (Wu et al. 2022), and a reduced prevalence of organisms that produce lipopolysaccharides (LPS) and trimethylamine N-oxide (TMAO) (Fig. 2). Additionally, the microbial profile of centenarians has been found to resemble that of younger adults (Pang et al. 2023). The genus *Ruminococcus* is particularly prominent in the microbiota of centenarians, irrespective of geographic or genetic background (Tuikhar et al. 2019), and its abundance has been positively correlated with high-fiber dietary intake ((Reva et al. 2023); (Salas-Perez et al. 2023). Furthermore, centenarians demonstrate a higher prevalence of environmental species, which are derived from soil, plants, and freshwater. This phenomenon may be associated with reduced antibiotic exposure and increased early-life interactions with natural environments (Franceschi et al. 2018). Notably, strains such as *Lactobacillus plantarum*, isolated from centenarians in Jiaoling, China, possess genes that are implicated in redox homeostasis (e.g., *gpx, trxA*), thereby contributing to antioxidant functions (Wu et al. 2022).

Akkermansia muciniphila, Christensenella, and *Methanobrevibacter smithii* have been related to the maintenance of mucosal integrity and energy homeostasis in individuals with exceptional longevity (Palmas et al. 2022). A longitudinal study conducted with centenarians of Hainan, China demonstrated compositional changes in the gut microbiota in the months leading up to death, thereby underscoring its dynamic plasticity and potential influence on healthspan extension (Luan et al. 2020). Thus, the centenarian microbiota may serve as a promising model for exploring microbe–epigenome interactions relevant to healthy aging.

Epigenetic mechanisms influenced by the gut microbiota

The microbiota produces a diverse array of epigenetically active metabolites, including short-chain fatty acids (SCFAs), bile salts, amino acids, vitamins, and lipopolysaccharides (LPS). These metabolites function as signaling molecules that facilitate epigenetic modifications, thereby influencing transcription, host cell translation, and histone accessibility, all without altering the sequence of the genetic code (Krautkramer et al. 2016). Additionally, biomolecules generated through bacterial metabolism can act as substrates for the enzymatic synthesis of "erasers" and "writers", regulating epigenetic processes (Sharma et al. 2020). The activity of these epigenetic modifiers is contingent upon the availability of the aforementioned bacterial compounds (Woo & Alenghat 2022).

DNA methylation is defined by the addition of methyl groups ($-CH_3$) to cytosine residues that precede a guanine base (5'CpG3') by DNA methyltransferases (DNMT), which may lead to gene silencing (Xu et al. 2023). DNMT activity depends on folate and other B-complex vitamins, acquired through dietary sources or synthesized by specific symbiotic bacteria, such as *Lactobacillus* and *Bifidobacterium.* These bacteria deliver S-adenosylmethionine (SAM), a critical component for methylation (Sharma et al. 2020). Genes responsible for folate synthesis are present in intestinal bacteria, many of which possess the complete set of genes required for the de novo synthesis of folate (Engevik et al. 2019). Research indicates a global decline in gene methylation with advancing age; however, this reduction is less pronounced in centenarians (Marcos-Pérez et al. 2021). DNA demethylation involves the removal of methyl groups through the action of TET (Ten-Eleven Translocation) enzymes. These enzymes require α-ketoglutarate as a cofactor to oxidize 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) (Wu & Zhang 2017).

The production of short-chain fatty acids by gut bacteria influences the levels of Acetyl-CoA and various Krebs cycle precursors, including α-ketoglutarate, fumarate, and succinate, thereby affecting TET enzyme activity (Woo & Alenghat 2022). Additionally, L-ascorbic acid, which is produced by *L. plantarum*, may function as a cofactor for TET enzymes during DNA demethylation, thereby contributing to the stabilization of epigenetic patterns (Pavlovic et al. 2023).

Post-translational modifications of histones, which are physically associated with chromatin as octamers (nucleosome), are influenced by variations in microbial metabolites, including methylation, acetylation, phosphorylation, acylation, lactylation, dopaminylation, and ubiquitination, among others. These modifications can facilitate both gene activation and silencing by altering the accessibility of chromatin through covalent bonds formed at lysine, arginine and other residues (Xu et al. 2023). Histone methylation, catalyzed by a variety of different methyltransferases (HMTs), can exert either an activating effect (e.g., H3K4) or a repressive effect (e.g., H3K9, H3K27), contingent upon the specific site of modification and the availability of SAM precursors (Gold & Shilatifard 2024).

Histone acetylation is mediated by histone acetyltransferases (HAT), which transfer acetyl groups from acetyl-CoA to lysine residues at the histone amino-terminal tail (Sharma et al. 2020). Acetate, a microbial-derived SCFA, can increase glycolytic flux and, after conversion to acetyl-CoA, provide acetyl groups for acetylation reactions. Histone acetylation and tumor growth inhibition in hepatocellular carcinoma, as well as Treg activation and anti-inflammatory responses, have been reported to be related to DNA methylation (Lei et al. 2025).

The removal of acetyl groups is carried out by histone deacetylases (HDACs), which act on the amino-terminal lysine residues of histones, leading to increased chromatin compaction and subsequent inactivation of gene expression (Sharma et al. 2020). HDACs are classified into five main groups: classes I, IIa, IIb, III and IV. The enzymes of classes I, II and IV are dependent on zinc ions (Zn^{2+}) and participate in a wide range of biological processes, including cell cycle regulation, cell differentiation and modulation of the immune response (Zhang et al. 2025). On the other hand, class III HDACs, known as sirtuins, are NAD-dependent enzymes and play crucial roles in DNA repair, cell senescence regulation and energy metabolism, being directly involved in mechanisms associated with celluriilar aging. In particular, SIRT1 (sirtuin-1) plays a fundamental role in biological aging pathways, as it deacetylates transcription factors such as p53 (tumor protein p53), FOXO3a (forkhead box O3a), NF-κB (p65) (nuclear factor kappa B) and PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1 alpha), modulating gene regulation and metabolism (Martins 2017). The deacetylation of p53, for instance, attenuates pro-senescence and pro-apoptotic pathways (Lo Cigno et al. 2023). SCFAs are well-documented as HDAC inhibitors, as they promote the production of essential metabolic substrates such as acetyl-CoA, which is critical for the regulation of histone acetylation (Kopczyńska & Kowalczyk 2024)).

Additionally, inositol phosphate, produced by bacteria such as *Escherichia coli*, has been shown to activate HDAC3 (Wu et al. 2020). Lysine crotonylation, a histone modification that has received limited attention in the literature, is found to be elevated at promoters and enhancers in mammalian cells (Sharma et al. 2020). SCFAs have been shown to enhance crotonylation, whereas a reduction in the intestinal microbiota induced by antibiotic treatment is correlated with a decrease in this modification (Fellows et al. 2018). Furthermore, various age-related diseases, including metabolic syndromes, Alzheimer's disease, and cancer, have been associated with disruptions in crotonylation activity (Yang et al. 2023).

Non-coding RNAs (ncRNAs) serve as significant regulators of gene expression in the bidirectional communication between microbiota and host organisms. They can be categorized into long non-coding RNAs (lncRNAs; > 200–300 bp) and small non-coding RNAs (< 200–300 bp), which include microRNAs (miRNAs), short interfering RNAs (siRNAs), and endogenous siRNAs (Sharma et al. 2020). ncRNAs that influence host phenotypes may be derived from the microbiota, while endogenous ncRNAs (expressed within cells and tissues) and exogenous ncRNAs (acquired through dietary sources) can also affect the composition and selection of the microbiota (Malmuthuge & Guan 2021). For instance, the administration of synthetic miR-30d in mice with induced autoimmune encephalomyelitis increased the expression of the lactase enzyme gene in *Akkermansia muciniphila*, and enhanced its population abundance. This intervention led to clinical improvements in the animals, attributed to an increase in regulatory T cells (Tregs) (Y. Liu et al. 2021a, b). Furthermore, food and feed sources are recognized as providers of exosomal miRNAs, also referred to as xeno-miRNAs, which play a role in influencing microbial selection and competitiveness. Notably, the supplementation of miRNAs derived from the ginger plant was found to promote the proliferation of *Lactobacillus* spp., thereby facilitating tissue repair of the intestinal barrier through the expression of interleukin-22 and the activation of the signaling pathway mediated by the aryl hydrocarbon receptor (Teng et al. 2018).

Microbial metabolites and epigenetic modifications in healthy aging among centenarians

The metabolic profile of the gut microbiota, influenced by the interplay of genetic and environmental factors, serves as a crucial mediator of epigenetic mechanisms associated with age-related diseases (Huang et al. 2021); (Díez-ricote et al. 2021)). Various metabolites derived from the microbiota, such as SCFAs, p-cresol, TMAO, LPS and secondary bile acids, are integral to immune modulation, metabolic responses, and antitumor mechanisms (Table 1). These metabolites significantly impact the continuum between physiological and pathological aging (Huang et al. 2021); (Díez-ricote et al. 2021).

SCFAs, including acetate, propionate, butyrate, and valerate, are generated through the anaerobic fermentation of dietary fibers by the gut microbiota. These compounds serve as inhibitors of class I and II HDACs, thereby activating genes that are integral to immune, metabolic, and antitumoral pathways (Pérez-Reytor et al. 2021). Among these SCFAs, butyrate has been the subject of extensive research due to its diverse roles, which include the regulation of genes associated with oxidative stress management, such as FOXO3a, SOD2, and catalase. Additionally, butyrate is known to reduce the levels of reactive oxygen species and enhance mitochondrial function (Rose et al. 2018; Tang et al. 2022). Furthermore, butyrate has been shown to downregulate the expression of pro-inflammatory genes, including IL-1β, IL-6, IL-8, and CCL2 (Pedersen et al. 2023), modulate leptin secretion, and upregulate genes such as *Glut4,* Irs1, *Pdx1* and *MafA*, which are associated with weight regulation and insulin sensitivity as observed in a rat model (Tang et al. 2022). Cohorts of centenarians are enriched with of SCFA-producing taxa, as well as higher production of these metabolites, when compared to young or elderly control groups of typical aging (J. Cai et al. 2022) (Fig. 3).

In contrast, TMAO is a well-established biomarker for cardiovascular disease, identified in both animal and human models. TMAO is synthesized from dietary precursors, including choline, betaine, and

Table 1 Metabolic differences associated with the microbiota of centenarians and their epigenetic aspects

Metabolite/ Metabolic pathway and Profile in centenarians	Sample	Epigenetic mechanism and physiological response	References
SCFA – Acetic acid ↑	Feces	Acetyl-CoA substrate;—Histone acetylation- Inhibition of Class I HDACs and activation of HATs;	Bradshaw, (2021); J. Cai et al., (2022)
SCFA – Propionic acid ↑	Feces	Histone acetylation via acetyltransferase activation Inhibition of Class I HDACs	Park et al., (2023); J. Cai et al., (2022)
SCFA – Butyric acid ↑	Feces	Class I (e.g., HDAC1, HDAC2, HDAC3) and Class IIa (e.g., HDAC7, HDAC9) inhibition – AMPK activation	D. Cai et al., (2016); J. Cai et al., (2022)
SCFA – Valeric acid ↑	Feces	Inhibition of HDACs	D. Cai et al., (2016); J. Cai et al., (2022)
SBA ↑	Feces	Lithocholic acid: ↓ Inflammatory responses ↑ Expression of DUSP5 and TRAF5	D. Cai et al., (2016); Li et al. (2024)
TMAO ↓	Feces	↑ miR-21-5p, miR-30c-5p ↓ PER2 gene expression → circadian disruption, metabolic syndrome, CVD ↑ PRMT5 (aberrant methylation) ↓ SIRT3 and SOD2 → ↑ oxidative stress	W. Liu et al., (2021a, b); J. Li et al., (2022a, b); Díez-ricote et al., (2021)
p-Cresol ↓	Urine	Association of p-cresyl sulfate, derived from p-cresol with increased expression of miR-21 and activation of HIF-1α in the development of renal carcinoma; Alters miR-146b-5p, miR-223-3p expression; Disrupts endothelial repair; ↓ CREB phosphorylation and ↑ Rac-1 in hippocampus (neurotoxic)	Wu et al., (2019); D. Cai et al., (2016) Guerrero et al., (2020); Tevzadze et al., (2020)
LPS ↓	Blood plasma	↓ H3 phosphorylation/acetylation in COX-2 promoter → macrophage activation ↓ H3K4me3, H3K36me3 → inflammatory response ↓ H3K4me1 → epigenomic memory for future stimuli ↓ repression from SIRT-1	Jayashree et al., (2014); Chiariotti et al., (2016); Martins, (2017); Carrera-Bastos et al., (2018)

An upward arrow (↑) denotes an increase, while a downward arrow (↓) denotes a decrease, within the context of healthy aging

L-carnitine, which are nutrients prevalent in animal-derived foods. These precursors are metabolized by the gut microbiota into trimethylamine (TMA), which is subsequently oxidized to TMAO by hepatic flavin-containing monooxygenases (FMOs) (Díez-ricote et al. 2021). TMAO has been associated with systemic oxidative stress and inflammation, primarily through the activation of the NF-κB pathway. Notably, TMAO levels are found to be lower in centenarians, indicating a potentially protective metabolic profile (C. Li et al. 2022a, b); (Matacchione et al. 2024) (Fig. 3).

Similarly, circulating LPS levels, a component of the outer membrane of Gram-negative bacteria, was significantly lower in Italian centenarians (Carrera-Bastos et al. 2018). LPS is a potent inducer of the inflammatory cascade, promoting the expression of genes such as cyclooxygenase-2 (COX-2). Once translocated, LPS can enter systemic circulation and reach the brain parenchyma, thereby activating the NF-κB signaling pathway, upregulating miRNA-146a and miRNA-155A, and transmitting pro-inflammatory signals from the gut to the brain. This mechanism has been implicated in the pathogenesis

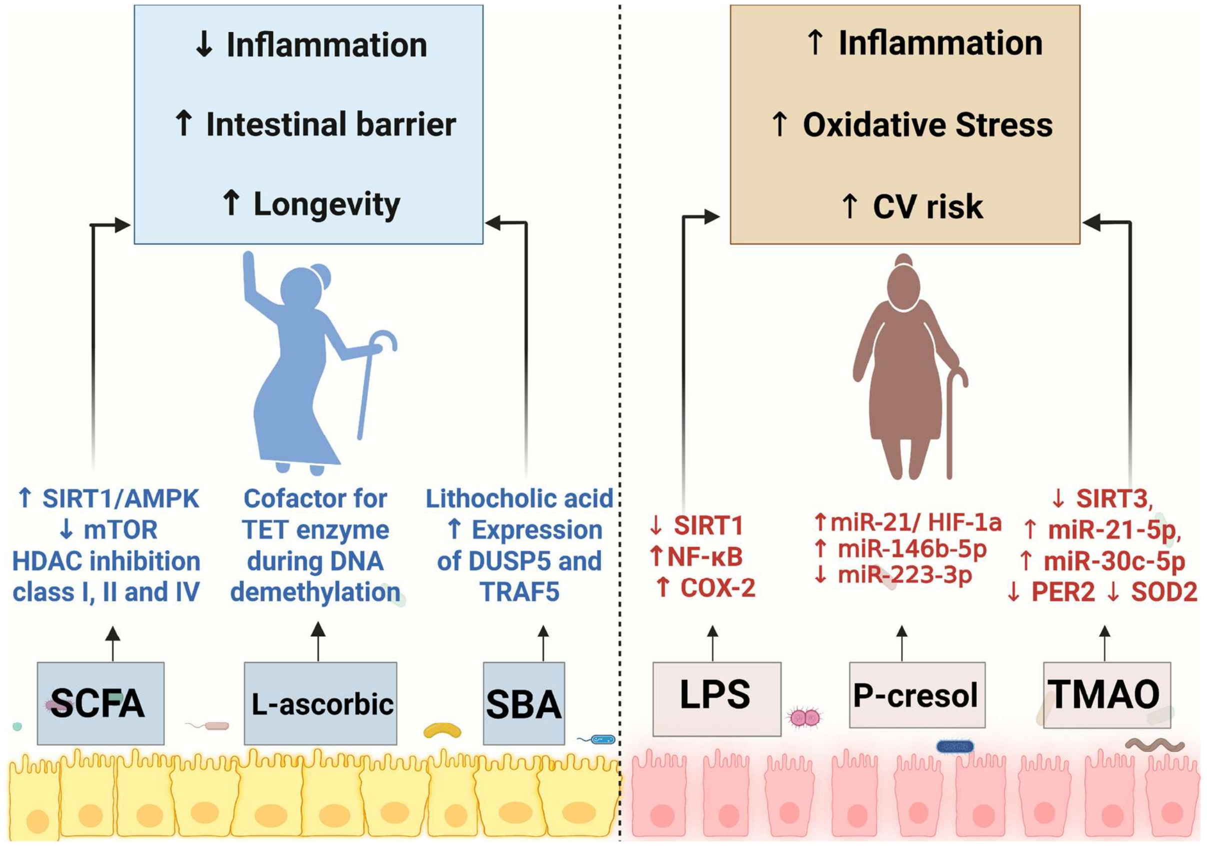


Fig. 3 Epigenetically active microbial metabolites modulate host physiology and longevity Beneficial microbial metabolites, such as short-chain fatty acids (SCFAs) and secondary bile acids (SBAs), exert epigenetic regulation by modulating histone acetylation, sirtuin activity, and signaling pathways (↑ SIRT1/AMPK, ↓ mTOR, ↑ DUSP5/TRAF5), leading to improved intestinal barrier integrity, reduced inflammation, and enhanced longevity. In contrast, detrimental metabolites like lipopolysaccharides (LPS) and trimethylamine-N-oxide (TMAO) promote pro-inflammatory and oxidative stress pathways (↑ NF-κB, ↑ COX-2, ↓ SIRT3, ↓ SOD2) and deregulate microRNAs (↑ miR-21-5p, ↑ miR-30c-5p) and circadian genes (↓ *PER2*), thereby increasing cardiovascular and metabolic risk. Elevated levels of SCFAs and SBAs are characteristic of centenarians, while reduced LPS and TMAO are associated with protection against chronic inflammation, oxidative stress, and cardiometabolic dysfunction. Abbreviations: AMPK, *AMP* activated protein kinase, *COX-2* cyclooxygenase-2, *CV risk* cardiovascular risk, *DUSP5* dual specificity phosphatase 5, *HDAC* histone deacetylase, *HIF-1α* hypoxia-inducible factor-1 alpha, *LPS* lipopolysaccharide, *miR* microRNA, *mTOR* mechanistic/mammalian target of rapamycin, *NF-κB* nuclear factor kappa B, *PER2* period circadian regulator 2, *SBA* secondary bile acid, *SCFA* short-chain fatty acid, *SIRT1/SIRT3* sirtuin-1/-3, *SOD2* superoxide dismutase 2, *TET* ten-eleven translocation (DNA demethylase), *TMAO* trimethylamine N-oxide, *TRAF5* TNF receptor-associated factor 5. Arrows: ↑ increase; ↓ decrease. Abbreviations: *Acetyl-CoA* acetyl coenzyme A, *AMPK* AMP-activated protein kinase, *CVD* cardiovascular disease, *COX-2* cyclooxygenase-2, *CREB* cAMP response element-binding protein, *DUSP5* dual specificity phosphatase 5, *HAT* histone acetyltransferase, *HDAC* histone deacetylase, *HIF-1α* hypoxia-inducible factor-1 alpha, *H3K4me1/H3K4me3/H3K36me3* histone H3 lysine 4 mono-/tri-methylation and lysine 36 tri-methylation (histone marks), *LPS* lipopolysaccharide, *miR* microRNA (e.g., miR-21-5p, miR-30c-5p, miR-146b-5p, miR-223-3p), *mTOR* mechanistic/mammalian target of rapamycin, *PER2* period circadian regulator 2 *PRMT5* protein arginine methyltransferase 5, *Rac-1* Ras-related C3 botulinum toxin substrate 1 (small GTPase), *SBA* secondary bile acid, *SCFA* short-chain fatty acid (e.g., acetate, propionate, butyrate, valerate), *SIRT3* sirtuin-3 (NAD$^+$-dependent deacetylase), *SOD2* superoxide dismutase 2, *TMAO* trimethylamine N-oxide, *TRAF5* TNF receptor-associated factor 5

of Alzheimer's disease (Alexandrov et al. 2019). Furthermore, LPS contributes to neuroinflammation by enhancing histone H3 phosphorylation and acetylation at Ser10 and Lys14 (H3S10phK14ac) in the hypothalamus and hippocampus, with promoter enrichment observed in genes such as IL-6 (Martire et al. 2019). LPS is considered a critical inhibitor of SIRT-1, which may contribute to chronic inflammation, metabolic disturbances, as increased dyslipidemia, and immune and autoimmune dysregulation (Martins 2017). Interestingly, increased and sustained levels of SIRT-1 have already been reported in centenarians, particularly in the hippocampal region (Omura et al. 2011).

The secondary bile acid pathway has been found to be enriched in centenarians (Sato et al. 2021), with several previously uncharacterized isoforms of lithocholic acid. Secondary bile acids are initially synthesized from cholesterol in the liver and subsequently secreted with bile. They undergo chemical transformations facilitated by the intestinal microbiota, specifically by bacteria possessing the *bai operon* (secondary bile salt bacteria), which encodes a set of proteins responsible for the enzymatic removal of the 7α-hydroxyl group from primary bile acids (Kiriyama & Nochi 2023). Notably, lithocholic acid is a significant metabolite investigated in the context of caloric restriction, demonstrating effects on lifespan extension in murine models (Qu et al. 2025), as well as modulating immune cell activity by attenuating inflammatory responses (Li et al., 2024). Various bacteria of centenarians' microbiota exhibit potential probiotic properties and are involved in the transformation of secondary bile salts, including *Clostridium* cluster XIVa, *Bacteroides fragilis, B. vulgaris, and Ruminococcus* (Sato et al. 2021) (Fig. 3).

Translational Potential: Epigenetically Guided Gerobiotic for Healthy Aging

Aging and influence both the prevention and treatment of neurological, metabolic, tumor-related, and skin-aging diseases (Mahamud et al. 2025; Choudhary et al. 2023).

Traditional probiotics primarily consist of lactic acid-producing bacteria, such as those belonging to the genera *Lactobacillus* and *Bifidobacterium*, which are commonly found in foods like yogurt and in breast milk (Abouelela & Helmy 2024). In contrast, new generation probiotics (NGPs), including *Faecalibacterium prausnitzii*, *Roseburia* spp., *Akkermansia muciniphila*, and *Bacteroides fragilis* (Al-Fakhrany & Elekhnawy 2024), are regarded as living biotherapeutic products and are currently subjected to regulatory investigations concerning their pharmacokinetics and pharmacodynamics (Abouelela & Helmy 2024). Key areas of interest in the study of probiotics related to longevity include metabolic enhancement, reduction of inflammatory profiles, and improved antioxidant responses. We highlight that probiotics include both Gram-positive and, to a lesser extent, Gram-negative bacteria; however, the majority of probiotics that are widely tested and reported in foods and dietary supplements belong to the Gram-positive group, particularly lactic acid bacteria (Al-Fakhrany & Elekhnawy 2024).

In the metabolic context, both centenarians and individuals undergoing caloric restriction exhibit low levels of IGF-1 (Insulin-like Growth Factor 1) and insulin, accompanied by enhanced insulin sensitivity (Palmas et al. 2022). Centenarians also present with lower fasting blood glucose and glycated hemoglobin levels compared to their co-residents (Ji et al. 2022). This phenomenon has been attributed to an increased abundance of butyrate-producing microbiota, which inhibit HDACs and upregulate insulin gene expression in pancreatic islets through H3K18 butyrylation at the promoter region (Wang et al. 2022). Furthermore, administration of *Akkermansia muciniphila* for three months in a double-blind clinical trial enhanced insulin sensitivity and reduced plasma cholesterol levels in overweight individuals (Depommier et al. 2019). This genus represents a key biomarker of the centenarian microbiota and has demonstrated probiotic potential in modulating the GH/IGF-1/ insulin axis (Table 2).

From an immunological perspective, centenarians exhibit a lower Th17/Treg cell ratio compared to elderly individuals, indicating a more youthful immune profile (Zhou et al. 2022). *L. rhamnosus* has been shown to promote the balance of this ratio, while *L. acidophilus* suppresses the production of pro-inflammatory cytokines, including IL-6, TNF-α, IL-1β, and IL-17 (Sapra et al. 2021; Park et al. 2018), highlighting its potential as a probiotic agent. Furthermore, the combination of *L. acidophilus* and *B. longum* inhibited COX-2 expression in a

Table 2 Epigenetic and gene expression particularities described in (super) centenarians associated with probiotics

Epigenetic modification	Physiological response	Probiotics	Reference
↑ mRNA of genes encoding intestinal junction proteins (e.g., *Claudin* and *ZO-1*)	Reinforcement of intestinal barrier, decreased permeability, immune balance, and reduction of excessive inflammatory response	*Bifidobacterium animalis*, *B. breve*, *B. longum*, *Lactobacillus fermentum*, *L. caseii*	Yang et al., (2023); Ren et al., (2021)
↓ Th17/Treg ratio	Anti-inflammatory state, decreased intestinal inflammation, associated with healthy aging	*Lactobacillus rhamnosus*	Sapra et al., (2021)
↓ Growth hormone (GH)/insulin-like growth factor (GH/IGF-1/insulin system)	Increased insulin sensitivity, decreased systemic inflammation, tumor protection	*Akkermansia muciniphila*	Duran-Ortiz et al., (2021) Sapra et al., (2021) Shaheen et al., (2025)
↑ SIRT1	Resistance to oxidative stress, mitochondrial biogenesis, decreased pro-inflammatory cytokines, longevity in animal models	SLAB51 (multi-strain: *Streptococcus thermophilus, B. longum, B. breve, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus, L. brevis*)2. *L. fermentum*3. *Lacticaseibacillus paracasei* PS117	Bonfili et al., (2018); Scuto et al., (2024)
↓ mTOR (mechanistic/mammalian target of rapamycin)	Pleiotropic effect: marker of aging, life expectancy, nutrient sensing, cell proliferation, decreased insulin resistance, caloric restriction benefits	*L. rhamnosus*, *L. acidophilus*, *L. reuteri*	Sebastiani et al. (2021); Mohseni et al., (2021)
Hypermethylation of DMR *MACROD2/SEL1L2* (negative correlation with BMI; lower abundance in obese individuals)	Epigenetic biomarker of obesity and metabolic health	*Ruminococcus* (genus)	Salas-Perez et al., (2023)
↓ factors associated with tumor cell proliferation and survival, such as Akt, phosphorylated PI3K, and NF-κB (breast cancer – animal model)	↑ SCFAs synthesis; ↑ diversity in gut microbiota composition	Inulin	Wu et al., (2023) Boyajian et al., (2021)
↑ Increased expression of IL-18, Muc2 (mucin 2), Itln1 (intelectin-1), and tight junction proteins ↓ Decreased mRNA expression of fatty acid synthase and glycerol-3-phosphate acyltransferase	↑ Increased synthesis of short-chain fatty acids (SCFAs) ↓ Reduced cecal pH ↓ Decreased serum lipid levels following a high-fat diet in mice	Fructooligosaccharides (FOS)	Yu et al., (2020). Takai et al., (2020). Cao et al., (2021). Matt et al., (2018).Lima et al., (2018)
↑ mRNAs of cortical histone deacetylases (HDAC1, HDAC2)	↑ levels of N-methyl-D-aspartate receptor in rat brains; ↑ levels of fecal mucins and butyrate in rats	Galactooligosaccharids (GOS)	Gronier et al., (2018) Okazaki & Katayama, (2019)

An upward arrow (↑) denotes an increase, while a downward arrow (↓) denotes a decrease, within the context of healthy aging dose-dependent manner in gastric and colorectal cancer cell lines, exhibiting effects comparable to the selective anti-inflammatory drug celecoxib (Nada et al. 2020).

The enhancement of the intestinal barrier is pivotal in mitigating LPS' translocation, thereby contributing to the promotion of longevity. A consortium comprising *L. fermentum, L. caseii, B. longum* and *B. animalis* has been shown to induce the overexpression of junctional proteins such as ZO-1 and occludin. Furthermore, when combined with dietary fibers, this consortium increased Claudin-1 mRNA expression by up to 20-fold (Ren et al. 2021), resulting in reduced intestinal permeability and decreased serum LPS levels (Fang et al. 2021). In a study involving elderly Thai participants, administration of a probiotic combination containing *L. paracasei* HII01, *B. breve* and *B. longum* led to improvements in clinical parameters, including HDL, LDL, BMI, and elevated butyrate levels (Chaiyasut et al. 2022). Butyrate, a principal bacterial metabolite, is closely associated with enhanced intestinal permeability; its supplementation to increases the expression of Claudin-3 and Claudin-4, thereby restoring their levels following LPS-induced injury (H. Yan & Ajuwon 2017) (Table 2).

SIRT1 is recognized as a protective factor that mitigates oxidative stress and cellular senescence. SCFAs indirectly activate SIRT1 in a NAD+-dependent manner by increasing intracellular NAD+ availability; they also inhibit HDACs of classes I and II. Activation of SIRT1 has been associated with neuroprotection, regulation of oxidative stress, and suppression of pro-inflammatory pathways through modulation of p53 acetylation (Bonfili et al. 2018); Shats & Li 2020). *Bifidobacterium* and its metabolite acetate, a key SCFA, have been identified as significant activators of SIRT1 (Zhang et al. 2025). Furthermore, the probiotic consortium SLAB51, comprising nine strains, has been shown to activate SIRT1 in an Alzheimer's disease mouse model (Bonfili et al. 2018). Activation of SIRT1 and reduction of TNF-α were also observed following consumption of dadiah, a probiotic food fermented from buffalo milk with *L. fermentum* in mice with diabetic nephropathy (Amelia et al. 2023).

Other critical pathways involved in cellular aging that interact with one another include the mechanistic target of rapamycin (mTOR), an energy sensor that regulates cell growth, energy metabolism, and protein synthesis. Hyperactivation of mTOR is associated with pathological conditions such as neurodegeneration, cancer, and diabetes, whereas its inhibition has been consistently linked to lifespan extension in various animal models (Saxton & Sabatini 2017; S. H. S. Lee et al. 2022). Evidence suggests that increased production of SCFAs contributes to the activation of SIRT1 (Hsu et al. 2021), reduced activation of the IGF-1/insulin signaling axis, and activation of AMPK. AMPK, in turn, directly inhibits the mTORC1 complex, thereby promoting beneficial effects on cellular homeostasis and healthy aging (Mazucanti et al. 2015); (Igarashi & Guarente 2016) (Table 2).

There is also evidence that prebiotics contribute to the selection of beneficial host microorganisms through dietary interventions aimed at microbiota modulation, which, in turn, affects the pool and selection of microorganisms, as well as their epigenetically active metabolites, such as SCFAs and methyl-group donors (Chenhuichen et al. 2022). Prebiotics are nondigestible, selectively utilized substrates—such as fermentable oligosaccharide fibers containing fructose (e.g., inulin-type fructans and fructooligosaccharides) and those containing galactose (e.g., galactooligosaccharides) (Smolinska et al. 2025). It is noteworthy that dietary patterns in regions with a high prevalence of centenarians, such as the "Blue Zones," are rich in prebiotic components, including dietary fibers, resistant starches, and polyphenols (Davinelli et al. 2025). The most significant contribution currently reported from prebiotic use is increased gut microbiota diversity and increased SCFA production (Table 2).

It is recognized that inulin supplementation can increase the diversity of intestinal microorganisms and significantly promote the growth of bacteria of the genus *Bifidobacterium* and SCFA-producing microorganisms (Birkeland et al. 2020; Kiewiet et al. 2021). A study with pregnant female mice fed a high-fat diet and given inulin showed improved glucose intolerance in their offspring and induced differential DNA methylation in genes such as *Wnt5a* (wingless-type MMTV integration site family, member 5A) and *Pi3k (phosphoinositide 3-kinase)*, compared with offspring whose mothers did not receive inulin (Zhang et al. 2020). Aged mice fed an inulin-rich diet exhibited increased SCFA production compared with the low-inulin diet group, without a statistically significant reduction in the expression of inflammatory genes; however, a significant attenuation of microglial hyperreactivity was observed, as evidenced by reduced IL-1β levels following LPS stimulation (Matt et al. 2018).

Twelve weeks of fructooligosaccharide (FOS) supplementation in aged female rats resulted in increased butyrate production and differential expression of 19 genes associated with immune mechanisms, metabolic pathways, circadian cycle regulation, and redox status compared with the control group (Lima et al. 2018). Following FOS supplementation, Kato et al. (2022) highlighted substantial interindividual variability in absolute fecal bacterial counts and fructose utilization, underscoring the need for personalized approaches to modulate the intestinal microbiota.

Along the same lines, synbiotics should also be mentioned. They are defined as a mixture of live microorganisms combined with selected substrates that enhance the growth of beneficial bacteria—that is, a synergistic union of prebiotics and probiotics (Smolinska et al. 2025). There are only a few studies investigating epigenetic markers modulated by synbiotics in humans, with prebiotics and probiotics being more extensively studied. Most studies in animal models show superior outcomes in SCFA production, reduced colonic inflammation, and improvements in insulin and lipid markers with synbiotics compared to probiotics or prebiotics alone (Ke et al. 2019; Shinde et al. 2020).

Gadallah et al. (2021) demonstrated that the use of synbiotics over 12 weeks reduced hepatic expression of *YAP1(Yes-associated protein 1)* mRNA and *miR-1205*, while increasing the expression of *LATS1* (large tumor suppressor kinase 1) and *NF2* (neurofibromin 2) mRNAs and the lncRNA *SRD5A3-AS1 (steroid 5 alpha-reductase type 3 antisense RNA 1)*. Additionally, synbiotics decreased the percentage and stage of steatosis, inflammation, and fibrosis observed in rats with non-alcoholic steatohepatitis.

The use of a synbiotic (*Bifidobacterium animalis* subsp. *lactis* and *L. paracasei* subsp. *paracasei* DSM 46331 + oat β-glucan) in mice following a high-fat diet was shown to increase SCFAs and reduce total bile acids (Ke et al. 2019). A study using synbiotic supplementation (*Bacillus coagulans* + resistant starch from green banana) reported reductions in inflammatory markers such as C-reactive protein and IL-1β, increases in IL-10, and a significant rise in SCFAs (Shinde et al. 2020).

Taken together, these findings reinforce the need for additional experimental studies to elucidate the mechanistic links underlying epigenetic effects on metabolic, immunological, and neuromodulatory pathways induced by probiotics, prebiotics, and synbiotics.

Conclusions

In our study, we demonstrated that extreme longevity converges with lifestyles characteristic of Blue Zones and regions with a high prevalence of centenarians, favoring the selection of a functionally enriched gut microbiota that, through its metabolites, modulates epigenetic pathways essential for longevity and impacts metabolism, pro- and anti-inflammatory networks, the cell cycle, and antioxidant responses.

Centenarians have a more diverse microbiota than younger and typically aging elderly individuals, expanding the host's genetic and functional repertoire, with a predominance of SCFA producers, a lower burden of inflammatory metabolites (TMAO, *p*-cresol, LPS), and the production of microbial antioxidants (e.g., L-ascorbic acid). These metabolites influence the activity of epigenetic enzymes, favoring reduced systemic inflammation (downregulation of NF-κB/COX-2 and modulation of the Th17/Treg balance), preservation of cellular regulatory axis (SIRT1/p53), improved glucose metabolism (modulation of SIRT1/AMPK and mTOR, and attenuation of the IGF-1/insulin axis), decreased intestinal permeability (ZO-1, occludin, and claudins), and an improved redox state—characteristics congruent with reduced biological age. Centenarians appear to preserve the SIRT1 regulatory axis by contributing bacterial metabolites that increase NAD^+ levels and reduce SIRT1 inhibitors, such as LPS and TMAO.

Together, these pathways highlight potential biomarkers for further investigation within the microbiota–epigenetics–aging axis, representing an effort to identify the mechanistic links underlying the gut microbiota's impact on healthy aging. These findings support the use of gerobiotics, probiotics aimed at mitigating age-associated diseasessuch as *Akkermansia muciniphila*, *Lactobacillus/Bifidobacterium* consortia, and multispecies formulations, as strategies anchored in the microbiota–epigenome–aging axis. Thus, centenarians constitute a promising study model for elucidating epigenetic mechanisms associated with the microbiota in aging and a source of bioprospecting for gerobiotic selection in the context of precision medicine. However, we acknowledge the limitations of the Blue Zones as a heuristic model and the reliance on observational studies. This work is exploratory and reinforces the need for clinical trials and longitudinal studies evaluating epigenetic outcomes mediated by the microbiota and longevity, to further explore the hypotheses raised here.

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Declarations

Conflict of interest The authors declare no competing interests.

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