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Review Article

The Gut Microbiota as a Master Regulator of Health span and Longevity: Mechanisms and Therapeutic Potential

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Abstract

Aging is a complex biological process regulated by genetic, environmental, and lifestyle factors, with gut microbiota has recognized as a key determinant of health span and longevity. The present review integrates recent information from animal and human studies to describe the role of gut microbiota in the process of aging and its association with age-related deficit. A comprehensive search was conducted, underlying the mechanisms of microbial dysbiosis associated with "inflammaging," impaired gut barrier function, and disrupted host-microbe communication. This analysis demonstrates that loss of microbial diversity and shifts in microbial composition are hallmarks of aging that contribute to chronic inflammation and age-related disorders. Conversely, a healthy and diverse microbiota, as seen in long-lived individuals, is associated with improved metabolic and cognitive function. The review also examines current and emerging therapeutic strategies aimed at modulating the gut microbiome to facilitate healthy aging, including diets, prebiotics, probiotics, and fecal microbiota transplantation (FMT). Lastly, the potential of personalized microbiome medicine and the development of next-generation probiotics are also viewed as promising avenues to increase health span and quality of life in the elderly. This review provides a general overview to find the pivotal status of the microbiome in biology of aging and its therapeutic value as an age-related physiological decline target.

Keywords: Gut microbiota, Longevity, Health span, Dysbiosis, Fecal microbiota transplantation (FMT).

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1. Introduction

Ageing is a universal, yet profoundly heterogeneous, biological process characterized by a progressive accumulation of molecular and cellular damage, leading to compromised physiological function and increased susceptibility to disease. While often perceived as a phenomenon of the later stages of life, its roots are embedded in cellular and molecular events that commence much earlier (1,2). The intrinsic aging process is a result of a complex interaction between epigenetic modification, genetics, cellular damage, mitochondrial decline, and loss of proteostasis and finally declining organ function at the system level. Although genetics sets the boundaries of an organism's maximum lifespan, aging is quite plastic as a process. Growing evidence highlights the pivotal role of environmental and lifestyle determinants such as diet, exercise, and psychosocial stress that can modulate basic aging processes and have a dramatic influence on health span and longevity (3,4). Cellular senescence has also been recognized as a major contributor to age-related diseases, one of the strongest features of the process. Originally designed to be an effective anti-tumor mechanism to block cells' division once they become non-functional, the persistent gathering of senescent cells becomes deleterious to the microenvironment of the tissue (5,6). This deleterious effect is primarily mediated through the senescence-associated secretory phenotype (SASP), a complex secretome comprising pro-inflammatory cytokines, chemokines, growth factors, and proteases. The SASP is a key instigator of "inflammaging," a chronic, low grade, sterile inflammation that is now recognized as a fundamental underpinning of most, if not all, age-related diseases, including neurodegeneration, cardiovascular disease, and metabolic disorders (7,8). Today, the gut microbiota is identified as a key interface between environmental exposures and host physiological outcome and has radically transformed thinking about healthy outcome and the process of aging. The architecture and functional capacity of the gut microbiome are subject to dynamic variation throughout life and show a marked correlation with host health status. A hallmark of biological aging is the development of gut dysbiosis, characterized by reduced microbial diversity, increased pro-inflammatory taxa, and a reduced complement of beneficial commensal microorganisms. This dysbiotic state is ever-more correlated with dysfunctional intestinal barrier function (leaky gut), activation of the systemic immune systems, and worsening of inflammaging, with resultant higher levels of mortality and morbidity (9). On the other hand, a healthy and metabolically rich microbiota, or enrichment of particular microbial signatures and useful resultant byproducts, including short-chain fatty acids (SCFAs), secondary bile acids, and polyamines, aligns strongly with long health span and long lifespan in model organisms and in centenarians (10). Despite the strides taken, a major deficiency exists in understanding the interplay between two major pillars of aging biology: systemic cellular senescence/SASP and gut microbiota dysbiosis, and their combined influence on distal organ systems. Even though the concept of "gut-organ axes" (e.g., gut-brain and gut-liver) is well known, the gut-skin axis represents an extremely intriguing yet insufficiently studied domain. The skin, being the body's largest organ and the primary physical barrier, acts not just as a location of intense senescent cells accumulation but also as a major receiver of microbial and inflammatory stimuli issuing from the gut. However, the precise molecular mechanisms whereby a dysbiotic

gut microbiome influences senescence of skin cells, or vice versa, how a senescent dermal microenvironment may alter the gut microbes' composition, are still mostly unsolved. Moreover, the prospective role of microbial metabolites e.g., short-chain fatty acids (SCFAs), in modulating the SASP of dermal cells and subsequent consequences on skin pathologies are essential unanswered questions. Therefore, the present study aims to analyze the evidence linking these connected systems to the pathogenesis of major skin diseases, including impaired wound healing, chronic inflammatory diseases of the skin such as psoriasis, and skin carcinogenesis. Finally, therapeutic potential of novel interventions, ranging from senolytics and xenomorphic to selective probiotics, prebiotics, and fecal microbiota transplant, are discussed with the hope of uncovering ways to modulate both senescent cells load and the gut microbes and combat skin decline of aging.

2. Chane in Gut Microbiota with Age

Following the progression of age, the architecture, diversity, and function of gut microbiota experience widespread and progressive modifications. One of the most reliable findings in gerontology is the overall decline in microbial diversity with age, usually a marker of compromised resilience and ecological instability of the gut microbiome. Reduced diversity is commonly associated with increased risk of infection, metabolic derangement, and increased inflammatory response (11-13), however, centenarians defy this pattern. Several studies have shown that exceptional longevity persons possess or surpass microbial alpha diversity, and it has been hypothesized that a stronger and greater microbiome is tied to increased health span. Taxonomic differences also display unique age related trends (13). In most older persons, decreases in Bacteroidetes are accompanied by increases in *Proteobacteria*, such as the *Escherichia* and *Klebsiella* genera. These microorganisms are mostly opportunistic pathogens and their enrichment, particularly in the small intestine, makes the organ susceptible to infection or inflammation by dysbiosis. Centenarians' gut microbiome is usually enriched with beneficial taxa such as *Akkermansia* and *Lactobacillus*. The microbes are similarly renowned for their roles in the maintenance of mucosal barrier, host immune regulation, and positive metabolic actions leaving their value as biomarkers of health aging (14,15). Functional profiling highlights the significance of these composition changes as well. The ability of the microbes to catabolize carbohydrate and generate amino acids has been shown to be lowered with aging, perhaps suggesting diminished metabolic diversity of the microbiome (15,16). Short-chain fatty acids, mostly butyrate, can be sustained in certain subjects, presumably through the persistence of fermentative species (17). Impairments of predominant SCFA-producing species like *Faecalibacterium prausnitzii* have been linked to impaired intestinal barrier function, heightened systemic inflammation, and susceptibility to frailty. All these findings are in agreement with the context that not only presence but the presence of certain microbial taxa but actually their metabolic activity is important to shape healthy aging trajectories (17,18).

3. Determinants of Microbial Dysbiosis in Aging

Lifestyle in terms of diet is the primary modulator of health of microbiome in aging subjects. Reduced dietary fiber intake due to loss of appetite, impaired mastication, or food limitation deprives substrate of health-boosting fermentative

bacteria. This results in reduced production of SCFAs, metabolites important for intestinal barrier function and regulation of the systemic immune system (13,19). Besides, polypharmacy is highly prevalent among the elderly with routine exposure to antibiotics, proton pump inhibitors, and other medications disturbing microbial stability either directly or indirectly. Such drug stresses reduce microbial richness and allow growth of opportunistic genera such as *Clostridium, Klebsiella*, and other pathobionts and thus create inflammatory and infection-promoting conditions (11,20,21).

Frailty and comorbidities trigger excess risk of dysbiosis. Chronic diseases such as type 2 diabetes, cardiovascular disease, neurodegeneration, and chronic kidney disease are inseparably linked with dysbiotic microbial communities through loss of protective taxa and increase of pro-inflammatory species (22). Frailty itself is a multi-factorial syndrome with scaffolding from decreased physiological reserve has been reported to correlate with most extreme loss of microbial diversity and resilience. Under these conditions, gut microbiota is no longer an anchoring partner but rather the inducer of systemic deterioration by means of decreased metabolism, ongoing inflammation, and disrupted host-microbe homeostasis. Discovery of such determinants of dysbiosis emphasizes the importance of holistic lifestyle, diet, and clinical treatment for maintaining microbial well-being as a basis for successful aging (table 1) (14,22).

Table 1. Key Determinants of Gut Microbiota Dysbiosis in Aging Population.

Topic	Key Finding	Reference
Review on effects of dietary fiber on microbiome and SCFA	Dietary fiber enhances SCFA production and plays a critical role in gut and immune health.	Fu J et al. (2022) - Dietary Fiber Intake and Gut Microbiota in Human Health (23)
Review on fiber–microbiome -host health relationship	Fiber promotes growth of beneficial bacteria (Bifidobacterium, Lactobacillus) and reduces inflammation.	Makki K et al. (2018 - The Impact of Dietary Fiber on Gut Microbiota in Host Health (24)
Microbiome changes in aging and mechanisms	Aging is linked to reduced microbial diversity and disruption in metabolic pathways.	Nagpal R et al. (2018) - Gut microbiome and aging: Physiological and mechanistic insights (25)
Microbiome changes in aging and frailty	Frailty is associated with altered microbial composition and increased pro-inflammatory taxa.	Escudero-Bautista S et al. (2024) Impact of Gut Microbiota on Aging and Frailty: A Narrative Review (26)
Microbiome alterations in frail vs. non-frail adults	Frail individuals show markedly reduced microbial diversity and increased pathogenic taxa.	Wen NN et al. (2024) - Gut microbiota changes associated with frailty in older adults (27)
Dietary fiber intervention and short-term microbiome changes	High-fiber diet increases SCFA-producing bacteria and improves microbial profile.	Oliver A et al. (2021) - High-Fiber, Whole-Food Dietary Intervention Alters the Human Gut Microbiome (28)
Prospects of microbiome-based therapeutics in aging	Probiotics, prebiotics, and microbiome transfer may promote healthier aging and longevity.	Kadyan S et al. (2025) - Microbiome based therapeutics towards healthier aging and longevity (29)
Bibliometric analysis of microbiome research in Iran	Iranian microbiome research is expanding but remains mostly focused on clinical and epidemiological aspects.	Aazami et al. (2020) - The landscape of microbiota research in Iran; a bibliometric and network analysis (30)

4. Methods for Evaluating the Gut Microbiome

Sophisticated characterization of gut microbiota needs a multidisciplinary strategy beyond mere taxonomic profiling. High-throughput sequencing approaches such as 16S rRNA gene amplicon sequencing and shotgun metagenomics are valuable tools for inferring microbial diversity, richness, and functional potential across age groups (31,32). These approaches yield important information on the structure and ecological interaction of molecular communities but often functional data needs complementarity with meta transcriptomics, metabolomics, and metaproteomic. The application of such strategies as multi-omics leads to detailed understanding of microbial function, metabolite output, and interactions of hosts with microbes shaping biology of aging (33). In addition to these approaches, culture-dependent methodologies and gnotobiotic animals are valuable assets for confirming causal relationships of microbiota and physiology of hosts. Despite all these advances, a lack of standardization of sampling, sequencing, and bioinformatics approaches acts as a major bottleneck requiring standardized approaches for reproducibility and translational utility (31,33).

5. Mechanistic Pathways: From Dysbiosis to Physiological Aging

5.1. Inflammaging and Immune Dysregulation:

Inflammaging, or chronic low-grade inflammation, is a significant aspect of aging and is highly linked with dysbiosis of the gut microbiome. Dysbiosis compromises the integrity of the intestinal barrier, increasing permeability and allowing translocation of microbial components into systemic circulation such as lipopolysaccharides (LPS) and other pro-inflammatory mediators (34,35). This persistent microbial-stimulated activation results in the stimulation of the innate immune system, resulting in elevated circulating levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (36). In addition, during aging, the relative abundance of anti-inflammatory species such as *Bifidobacterium* and other protective commensals further decreases to exacerbate immune imbalance. Synergistically, these processes induce chronic systemic inflammation that exacerbates tissue injury, accelerates organ dysfunction, and increases vulnerability to age-related diseases such as cardiovascular disease, neurodegeneration, and metabolic disease (Figure 1) (13,36,37).

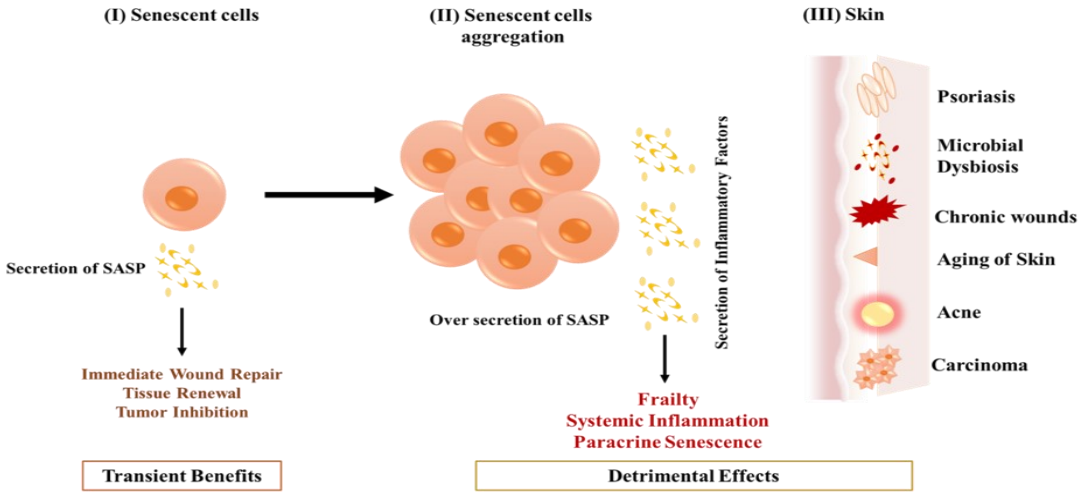

Fig 1. Cellular senescence on skin tissue. **(I)** Senescent cells release SASP factors that provide transient tissue benefits. **(II)** With their accumulation, excessive SASP secretion induces chronic inflammation, frailty, and paracrine senescence in neighboring cells. **(III)** SASP overproduction further contributes to the onset and progression of various cutaneous diseases.

5.2. Cellular Senescence and the Gut-Skin Axis: Cell senescence or permanent cell cycle arrest accumulates with every advancing age and maintains tissue dysfunction through the SASP. SASP constituents like pro-inflammatory cytokines, proteases, and growth regulators disrupt tissue homeostasis and regenerative capacity (7,38,39). New evidence indicates that microbial metabolites regulate senescence pathways locally in the gut and distally. Gut-skin axis represents one of the more concrete examples of such interaction: immune mediators and gut-derived metabolites that induce there are capable of modifying skin physiology, barrier function, wound repair, pigmentation, and pace of cutaneous aging. Dysbiosis breaking of the axis is able to speed senescence-associated skin disease, demonstrating the systemic feature of microbial balance in organ-specific aging (Figure 2) (40-42).

5.3. Metabolic Dysregulation: The microbiota of the gut highly controls the host metabolic networks by the creation of bioactive metabolites. SCFAs such as butyrate regulate energy homeostasis by enhancing mitochondrial function, inducing oxidative phosphorylation, and preserving insulin sensitivity. Polyamines such as spermidine induce autophagy and cell proteostasis, thereby supporting longevity pathways. Dysbiotic remodeling of the structure of SCFA-producing bacteria inhibition or reduced polyamines destabilizes these interfaces of metabolic networks, causing mitochondrial injury, disrupted nutrient sensing, and increased oxidative stress (12,43). Such types of metabolic disequilibrium not only foster physiological aging but also increase vulnerability to metabolic syndrome, sarcopenia, and other aging diseases. These mechanistic processes together demonstrate how community function and organization of gut microbiota are a vital factor in maintenance of systemic homeostasis and avoidance of adverse influences of aging (2,13,19,44).

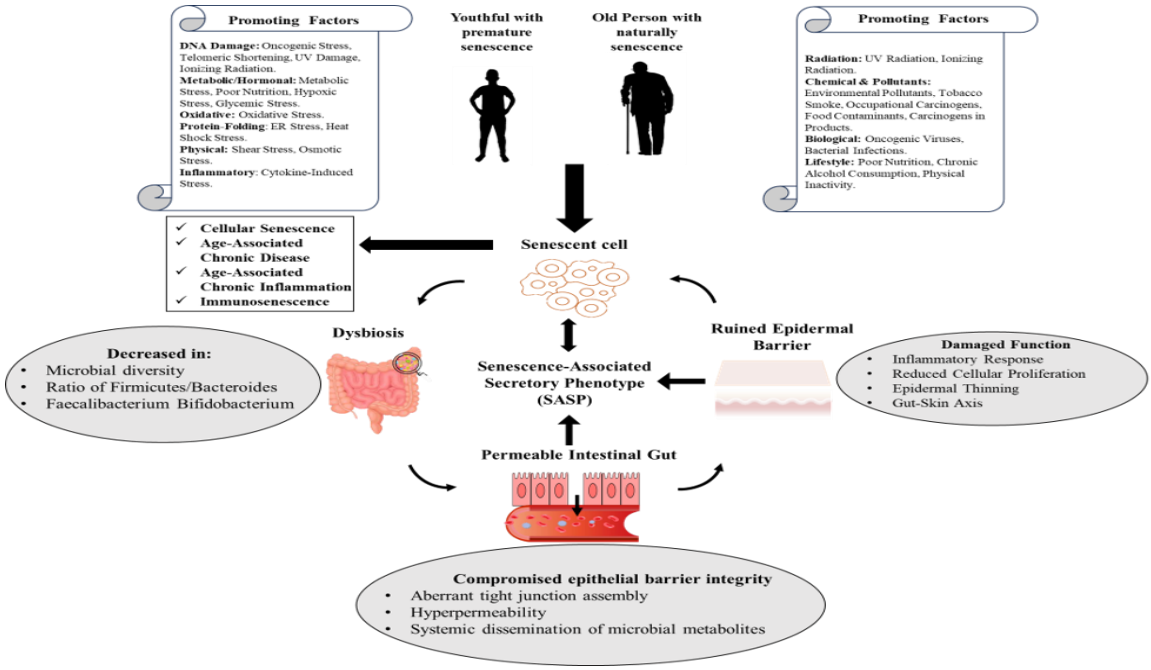

Fig 2. The gut microbiome, cellular senescence and systemic ageing, with an emphasis on skin health. Microbial dysbiosis, influenced by factors like UV radiation, disrupts intestinal barrier integrity, allowing pro-inflammatory mediators into circulation. Combined with SASP from senescent cells, this promotes chronic inflammation, immune dysfunction, and peripheral tissue decline, linking microbial imbalance to age-related deterioration and chronic disease.

6. Immunogenicity Assessment of Microbiome Targeted Interventions

The safety and therapeutic efficacy of microbiome modulating strategies depend critically on their immunological consequences. Immunogenicity is typically evaluated through profiling host responses at systemic and mucosal levels, including cytokine secretion patterns, T-cell activation, and modulation of regulatory immune subsets (45,46). State-of-the-art tools such as multi-parameter flow cytometry, single-cell RNA sequencing, and multiplex immunoassays have expanded the ability to capture host immune adaptation following probiotic, prebiotic, or fecal microbiota transplantation (FMT) (47). In addition, advanced experimental systems such as intestinal organoids co-cultured with immune cells provide physiologically relevant models for predicting host immune responses and screening for potential adverse effects. Incorporation of these immunological endpoints into both preclinical and clinical trials is essential to ensure not only the mechanistic understanding of host–microbe interactions but also the safety of microbiome-targeted interventions in vulnerable elderly populations (48).

7. Microbiome-Targeted Interventions and Longevity

7.1. Dietary and Lifestyle Interventions: Diet and lifestyle are the most readily accessible and impactful ways of influencing gut microbiota and healthy aging. Fiber, polyphenol, and other phytochemical-dense nutrition promote healthy phylotype growth of microbes and enhances secretion of SCFAs such as butyrate, acetate, and propionate (49,50). These end products of metabolism preserve intestinal barrier function, influence systemic immune homeostasis, and sculpt the host metabolism overall to enhance longevity. Besides diet, non-pharmacological modulators such as exercise and stress reduction also influence microbial composition, augmenting the diversity and resilience. These interventions are interesting to be applied due to their safety, efficacy, and system-level health implications throughout the elderly years (49,51).

7.2. Probiotics, Prebiotics, and Postbiotics: Microbial supplementation can be an encouraging method to prevent gut microbial homeostasis in the elderly years. Probiotics, i.e., *Lactobacillus* and *Bifidobacterium* strains, have been demonstrated to decrease systemic inflammation, restore intestinal epithelial barrier function, and favor metabolic well-being. However, suboptimal gut colonization, interindividual heterogeneity, and insufficient strong human clinical proof continue to restrict their long-term efficacy (52). Prebiotics are non-digestible substrates that selectively promote the growth and activity of advantageous microbes by supplying them with nutrients are synergistically capable of complementing probiotic action and supporting the synthesis of key metabolites like SCFAs (53,54). Hence, synbiotic products, known as combinations of probiotics with synergistic prebiotics, have yielded encouraging preclinical results (55). As such, the concurrent administration of Triphala (a polyherb) and *Lactobacillus fermentum*, for instance, was said to enhance health span and lifespan, suggesting additive or synergistic effect deriving from cooperative modulation of the microbial communities (56,57).

Postbiotics made of inert microbial metabolites such as butyrate, exopolysaccharides, and microbial peptides offer secondary therapeutic advantages through the instant delivery of bioactive molecules without engraftment involving live microbes (52). It is founded on a core paradigm shift in the aging sciences through microbial function and metabolite production prioritization instead of just the

survival of microbes (53). In fact, metabolomics had the potential to discover certain of the aging biomarkers such as NAD^+ and SCFAs that not only reflect the metabolic status of the host but can also be assumed to be precision targets for interventions (58). Through synergizing probiotic, prebiotic, and metabolite-focused intelligence, interventions can be constructed that act on the gut microbiota structure and functional output and healthy aging and health span increase (59).

7.3. Pharmacological and Nutraceutical Approaches: Pharmacologic and nutraceutical treatment represents yet another approach to microbiome-mediated aging manipulation. Senolytic drugs like Dasatinib and Quercetin have already been demonstrated to specifically eliminate senescent cells by inhibiting pro inflammatory SASP signals, which allows for tissue dysfunction (60). On the other hand, dietary compounds like spermidine and SCFAs were demonstrated to induce autophagy, recover mitochondrial function, and amplify lifespan increase in preclinical models (61,62). Though human intervention studies are not yet reported in the literature, available data suggest that combination of pharmacological interventions with diet-induced microbiome modulating regimens can be synergistic for age-related decline delay and longevity (63,64). These interventions suggest therapeutic potential of modulating microbial composition and function to systemic resilience and health span in aging (65).

8. Conclusions and Future Perspectives

Despite massive strides on the role of gut microbiota in aging, existing literature is riddled with numerous limitations. Several of the studies employ animal models or cross-sectional human data, restricting causality and human long-term outcome (53,66). The gut microbiome is characterized by a vast interindividual heterogeneity on the basis of genes, diet, lifestyle, and environmental exposures, and therefore precision therapy based on the individual's own signature microbial and metabolic imprint must be employed (34). Such new technologies like metagenomics, metabolomics, and artificial intelligence-driven analytics have the potential to drive the pace of discovery in strong biomarkers, mechanistic pathways, and tailored therapies (67). The gut microbiome is a master controller of aging biological processes, coordinating immune regulation, metabolic homeostasis, and inflammation. Microbial dysbiosis is strongly linked to the hallmarks of aging, whereas the typical microbial signatures in long lived animals are strong evidence for the therapeutic value offered by microbiome directed therapies (66).

Dietary modification, exercise, and medication are best researched anti-aging treatments and are backed by evidence which can restore microbic balance and promote a healthier intestinal environment (18,50,68). Prebiotics, synbiotics, and probiotics are promising, but there are limited and inconclusive human trials (69). Short and limited trial durations, heterogeneity of subjects, and safety evaluation in heterogeneous populations are some of the issues. Long-term, highly customized therapies, in tandem with multi-omics technology, and evaluation of life-style-based therapy as concurrent with pharmacologic and microbiome-guided therapies will be required in the future. Prior to discovering anti-aging drugs, evidence supports adopting healthy lifestyles e.g., adequately fed, daily exercise, adequate sleep, and no harms having most reproducible influences on health-span increase (18,50). Capitalizing on the promise of the gut microbiome, by way of these behavioral

interventions, can have the possibility of leading to tailored interventions which have the ability to not only extend lifespan but also the quality of life in the aging population.

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Conflict of interest
The authors declare no competing interests.

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Authors' contributions
Maryam Rahimi Foroudi and Ilnaz Sahragard performed the majority of collecting and writing of the data; Ilnaz Sahragard and Mohammad Amin Shayanfar designed and coordinated the research; and Maryam Rahimi Foroudi, Ilnaz Sahragard and Mohammad Amin Shayanfar wrote the paper.

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