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Mini Review

The Interplay of Diet, Microbiome and Longevity: Insights

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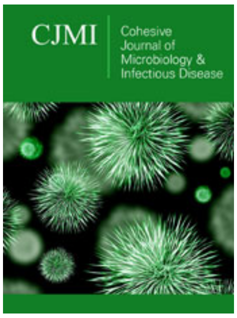

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Abstract

Diet, environmental exposures and aging profoundly influence the gut microbiota from early life onward. Emerging evidence underscores the microbiota's central role in regulating metabolism, immune function and inflammation-processes that are critical determinants of health and longevity. Gut bacteria generate Short-Chain Fatty Acids (SCFAs) that support intestinal barrier integrity, modulate immune responses and attenuate inflammation. Diets rich in fiber and polyphenols enhance SCFA production and promote microbial diversity, whereas low-fiber, high-fat diets disrupt microbial balance, contributing to metabolic dysfunction and age-related disease. Diet can potentially modulate the microbiota through epigenetic mechanisms, including DNA methylation and histone modifications, thereby influencing healthspan and lifespan. Nutritional interventions hold promise for mitigating age-associated microbial imbalances; however, disparities in socioeconomic status, dietary patterns and individual behaviours remain significant barriers to population-wide implementation. Further investigation into the complex interactions among diet, the microbiota and epigenetics is essential for developing personalized dietary strategies that foster healthy aging and extend longevity.

Keywords: Gut microbiome; Diet; Longevity; Aging; Healthspan; Short-Chain Fatty Acids (SCFAs); Inflammation; Epigenetics; Gut-brain axis; Metabolic health

Introduction

The gut microbiome changes as a person ages, with significant influences coming from factors such as the mode of birth (whether natural or Cesarean), nutrition, environment and life experiences [1-3]. Among these factors, nutrition plays a crucial and variable role, although dietary choices can have profound effects on the variety and function of gut microbes [4-6]. A well-functioning microbiome generates bioactive metabolites, such as Short- Chain Fatty Acids (SCFAs), which attenuate inflammation and contribute to healthy aging [7,8]. On the other hand, dysbiosis or the imbalance in microbial populations, is linked to a variety of illnesses, including those related to metabolism, cardiovascular health, the nervous system and the immune system [9,10]. This leads to a fascinating question: do gut microorganisms have the ability to actively impact the aging process and longevity?

Diet-microbiome links across the lifespan

Emerging research connects dietary habits and the microbiome to both healthspan-the duration of good health-and lifespan [11,12]. Nutrient-rich foods, such as those high in fiber, polyphenols and fermented products, can enhance microbial diversity and resilience, as well as metabolic and immune functions [13,14]. Conversely, diets that are high in sugar and unhealthy fats disrupt metabolism, promote inflammation and accelerate the aging process [15,16]. The microbiome influences digestion, immune response and brain function through its metabolites and communication between the gut and brain [17,18]. While we observe clearer correlations among these relationships, the precise molecular mechanisms underlying these associations remain unexplored. The cross-sectional study conducted in Japan, which spans the entire lifespan from infancy to extreme old age (1-100+ years), is crucial for understanding microbiome dynamics throughout life [3]. This research revealed that the diversity of gut microbes increases from infancy into early adulthood, remains stable during middle age and then declines after the age of 65, with more significant reductions observed after the age of 80. Beneficial microorganisms such as *Christensenellaceae* and *Akkermansia* flourish in the gut microbiome of those who live to be 100 or older, possibly playing a role in longevity [19,20]. At the same time, aging is characterized by higher ratios of potentially pathogenic or pro-inflammatory groups, i.e., *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia* and *Synergistetes*-with *Enterobacteriaceae*, *Alistipes* and *Ruminococcus gnavus* becoming more abundant in frail individuals [21,22]. The results emphasize the significance of different dietary elements throughout various life stages and stress the necessity for age-specific dietary plans aimed at promoting gut microbiota health for enhanced longevity.

Diet-microbiome-epigenetics nexus in aging

One of the emerging areas of research regarding the relationship between the microbiome and dietary factors involves epigenetic mechanisms that influence an individual's aging process [23,24]. Epigenetic alterations, including DNA methylation, modifications to histones and the role of non-coding RNA, modulate gene expression without changing the underlying DNA sequence [25,26]. Certain environmental factors, especially dietary components, can mediate these molecular changes, which are essential for longevity and overall health in aging individuals [27,28]. Nutrients like polyphenols, vitamins and fiber contribute to DNA repair and inflammation reduction, fostering beneficial epigenetic modifications that aid cellular recovery [29,30]. In contrast, unhealthy dietary patterns, particularly those high in fat and sugar, can lead to deleterious epigenetic alterations that hasten the aging process and increase the likelihood of age-associated diseases [31,32]. Investigating the connections among diet, epigenetics and the microbiome reveals their collective impact on the aging process. This highlights the importance of promoting diets that nurture a healthy microbiome and encourage epigenetic changes associated with longevity [33,34].

Personalized nutrition for microbiome health and healthy aging

Dietary intervention is an increasingly recognized concept that has proven effective in promoting a healthy gut microbiome, though its acceptance varies based on cultural, personal and economic factors [5,35]. Various approaches, including probiotics, prebiotics, synbiotics and Fecal Microbiota Transplantation (FMT), have been researched for their potential to restore microbial equilibrium in adults, particularly among older individuals. Nonetheless, their significance continues to be debated to this day [36,37]. Thus, the ongoing challenge lies in understanding how nutrition impacts microbiome composition to create personalized dietary strategies that may be more beneficial than microbial supplements from a public health perspective. While significant progress has been made in microbiome research, there remain many unanswered questions, especially in identifying causal relationships between microbiome changes and age-related illnesses. Most of the new research is correlational, which limits its therapeutic application and highlights the pressing need for more studies on the relationship between diet, microbiome and longevity, as illustrated in this brief communication. Connecting microbiome research with dietary studies and aging science aids in formulating effective approaches to enhance health and well-being. Shifting our attention from merely addressing age-related diseases to tackling their biological causes will mark a crucial advancement in alleviating healthcare challenges for aging populations.

Against this backdrop, the article first outlines the fundamental mechanisms that link diet, the microbiome and longevity, providing the basis for understanding their interconnected roles. It then examines how dietary restriction shapes microbiota-epigenome interactions that influence aging trajectories. Building on this, the discussion turns to the potential of probiotics in modulating systemic processes associated with age-related decline. The article concludes by considering the connections between dietary patterns, microbial composition and cognitive health, emphasizing their broader implications for brain aging.

Diet, Microbiome and Longevity: The Key Mechanisms

Recent studies indicate that diet has an impact on the gut microbiome, which subsequently affects aging by enhancing gut diversity, strengthening immunity, regulating genes and facilitating communication between the gut and brain [3-5,17,18,23-25]. One significant finding is the importance of microbial diversity in influencing lifespan [19,20]. A varied gut microbiota boosts metabolic health and immune functionality, both of which are crucial for healthy aging. The diversity of gut microbes is a key element in sustaining beneficial bacteria that aid in food digestion, maintain gut barrier integrity and modulate immune responses [8-10]. Additionally, a balanced microbiota helps hinder the growth of pathogens within the intestines as individuals age, thereby improving the symbiotic relationships among microorganisms [38-40].

Nutrition significantly contributes to the preservation of gut microbial diversity. Components such as fiber, polyphenols and fermented foods are recognized for their role in supporting healthy populations of gut microbes [41]. The generation of SCFAs like butyrate and acetate, which are beneficial for overall health and longevity, plays a crucial role in promoting microbiome health. Gut bacteria break down fiber to create metabolites that enhance immune function by boosting regulatory T-cells (Tregs) and decreasing inflammation [42,43]. SCFAs, particularly butyrate, may help mitigate age-related cognitive decline and Neurodegenerative Diseases (NDs) by alleviating neuroinflammation [44,45]. Furthermore, SCFAs are vital for preserving the integrity of the gut barrier, keeping harmful substances from entering the bloodstream and triggering systemic inflammation, which is a significant concern linked to aging [46,47]. Elevated levels of tight junction proteins or fungal metabolites in the bloodstream may suggest gut permeability, inflammation, dementia and frailty in older individuals [48,49]. A reduction in bacteria that produce SCFAs is often linked to heightened intestinal permeability [46,47]. SCFAs, particularly butyrate, provide energy to colon cells, enhance the gut barrier and may help alleviate inflammation as well as age-related illnesses [50,51].

A study showed that an eight-week Mediterranean diet boosts helpful gut bacteria such as *Faecalibacterium* prausnitzii, which generates SCFAs and promotes improved health [52,53]. This eating pattern also leads to a decrease in *Ruminococcus gnavus*, which is linked to gut inflammation [54]. Conversely, diets high in fat and sugar promote the growth of harmful bacteria like *Ruminococcus gnavus* and Proteobacteria, resulting in increased gut permeability and inflammation [55,56]. Chronic low-grade inflammation, often referred to as "inflammaging," is associated with aging and various health issues, including Cardio Vascular Disease (CVD), diabetes and NDs [57,58]. Making dietary modifications is essential for resolving inflammation. Consuming foods abundant in fiber, polyphenols and omega-3 fatty acids supports the growth of beneficial bacteria that combat inflammation [59,60]. Certain probiotics and prebiotics found in items like yogurt, kefir and fiber-rich vegetables have been demonstrated to lower the levels of pro-inflammatory cytokines [61,62]. A reduction in bacteria that produce SCFAs can contribute to inflammation among older individuals, whereas *Akkermansia* and *Christensenellaceae* are beneficial for SCFA production and immune support [63,64]. Therefore, the microbiome can potentially postpone the emergence of age-related illnesses by managing the immune system and decreasing overall inflammation, which in turn leads to healthier aging.

Microbiota-epigenome crosstalk in caloric restriction: implications for longevity

Research into aging's molecular pathways emphasizes the importance of Caloric Restriction (CR) in metabolic functioning and inflammation reduction [65,66]. CR mimetics or medicines that can extend lifespan while also improving health, continue to be an exciting topic of research in the realm of aging [67,68]. One of the emerging mechanisms by which CR exerts its beneficial effects is through modulation of the gut microbiome [69,70]. Aging is commonly associated with reduced microbial diversity, an expansion of pro-inflammatory taxa and a decline in beneficial commensals [71]. CR has been shown to reverse these age-related alterations by promoting a more diverse and balanced gut microbial community. In rodent models, CR increases the relative abundance of health-associated bacteria such as *Lactobacillus*, *Bifidobacterium* and *Akkermansia muciniphila*-the latter being linked to improved intestinal barrier function and attenuation of metabolic inflammation [72,73]. Simultaneously, CR reduces the prevalence of pathobionts and microbial signatures associated with systemic low-grade inflammation (termed "inflammaging") [74,75].

CR also enhances the microbial production of SCFAs, particularly butyrate and propionate [76]. These SCFAs are key microbial metabolites that influence host gene expression, modulate immune responses and support mitochondrial function [77]. Their beneficial effects are partly mediated through the inhibition of Histone Deacetylases (HDACs) and activation of G-Protein-Coupled Receptors (GPRs), such as GPR41 and GPR43 [78,79]. These combined actions contribute to maintaining gut barrier integrity and reducing systemic inflammation. Moreover, studies on CR mimetics-including resveratrol, metformin and rapamycin-demonstrate their capacity to recapitulate many of the microbiome-modulating effects of CR [80,81]. Collectively, these findings underscore the central role of the diet-microbiome axis in regulating host metabolism, inflammation and longevity.

Importantly, these microbiota-driven effects of CR extend beyond immune and metabolic regulation to include modulation of the epigenome, a critical layer of gene expression control during aging [82,83]. Epigenetic mechanisms greatly influence the aging process, with microbiome metabolites influencing the epigenome via mediating SCFA-induced DNA methylation or histone modification, hence modulating gene expression [84,85]. Butyrate inhibits HDACs, activating genes linked to longevity like FOXO3 (Forkhead box O3) and SIRT1 (Sirtuin 1) [86,87]. The Mediterranean diet raises SCFAs and lowers inflammation-related DNA methylation. CR helps beneficial bacteria, increasing histone acetylation and reducing SIRT6 methylation [88,89].

The role of probiotics in systemic aging processes

Significantly, probiotics can also change gene methylation linked to immunity and oxidative stress, improving cognition and reducing cellular aging [90,91]. Emerging evidence suggests that probiotics can have beneficial actions not only by modulating intestinal microbial community but also through epigenetic remodeling of host gene expression, especially in pathways linked to immune function, oxidative stress and neurocognitive health [92-94]. Certain probiotic species, such as *Lactobacillus* and *Bifidobacterium*, modulate the action of epigenetic enzymes like DNA Methyltransferases (DNMTs) and HDACs, thus modifying patterns of DNA methylation and histone modification [95,96]. For example, supplementation with *Lactobacillus plantarum* has been found to restore normal methylation levels at the promoter region of IL-6, a primary pro-inflammatory cytokine, to promote decreased systemic inflammation in aging models [97,98]. Concurrently, probiotics augment SCFAs availability, notably butyrate, a well-known HDAC inhibitor. Microbial metabolites improve the expression of antioxidant defense genes like SOD2 (Superoxide Dismutase 2) and GPX1 (Glutathione Peroxidase 1), effectively preventing oxidative stress, a key promoter of cellular senescence and neurodegeneration [99,100]. Redox homeostasis, immune tolerance and metabolic control are also maintained by SCFA-mediated epigenetic regulation. In addition, the Gut-Brain Axis (GBA) is a conduit through which probiotics exert their effects on brain health by epigenetically remolding [101,102]. Probiotic treatments have been associated with alterations in neuroprotective gene expression and methylation, such as BDNF (Brain-Derived Neurotrophic Factor), which is crucial for synaptic plasticity and cognition [103,104]. Studies in animals have shown that *Bifidobacterium longum* or *Lactobacillus rhamnosus* supplementation elevates hippocampal levels of BDNF, enhances memory performance and decreases anxiety-like behavior-effects that are very likely to be mediated at least in part through epigenetic mechanisms [105,106].

Together, these findings suggest that probiotics possess the capacity to modulate host epigenetic landscapes, thereby influencing key biological processes such as immune regulation, oxidative stress response and neuroplasticity. This positions probiotics and other microbiome-targeted interventions as promising strategies for enhancing cognitive resilience and promoting healthy aging through the epigenetic modulation of aging-related molecular pathways. The evidence further supports the notion that gut-directed dietary interventions may exert systemic effects on aging and longevity by reshaping the epigenome in a manner that favors cellular homeostasis and functional preservation.

Interlinking diet, microbiota and cognitive health in the aging brain

The GBA communication between the microbiota and the aging process is critical [107,108]. Gut microorganisms produce neurotransmitters like serotonin and Gamma-Amino Butyric Acid (GABA), which are essential for mood, cognitive function and neuroplasticity [109,110]. Dysbiosis, an imbalance of gut bacteria, has been linked to neurological diseases such as depression, anxiety and cognitive loss [111,112]. Research suggests that food choices have a direct impact on the microbiome's ability to generate these neurotransmitters. A fiber-rich diet increases SCFA production, which benefits neuroinflammation and cognitive health [5-7].

The study found that a ketogenic diet boosts the amounts of *Akkermansia muciniphila* and *Lactobacillus*, which aid in mitochondrial function and neuroprotection [113,114]. The Mediterranean diet has been proven to promote the growth of *Bifidobacterium* and *Lactobacillus*, which therefore improves serotonin metabolism and memory [115,116]. Polyphenol-rich foods, such as berries and green tea, also help to boost *Bifidobacterium* and prevent oxidative damage, which impairs cognitive performance [117,118]. Probiotics may assist in repairing neurotransmitter synthesis pathways, lessen stress levels and reverse cognitive decline [119,120]. Nonetheless, these findings have identified diet-microbiome-longevity integration as a key area for promoting healthy aging. Nutrition, the microbiome and longevity interact in complex ways, affecting microbial diversity, SCFAs, immunity, epigenetics and the GBA. A diet rich in microbial diversity and beneficial metabolites is essential for graceful aging. As shown in Figure 1, the flowchart maps the mechanistic pathway linking diet, microbial diversity and lifespan regulation Although more research is needed, current evidence shows that dietary choices play a major role in promoting longevity and well-being.

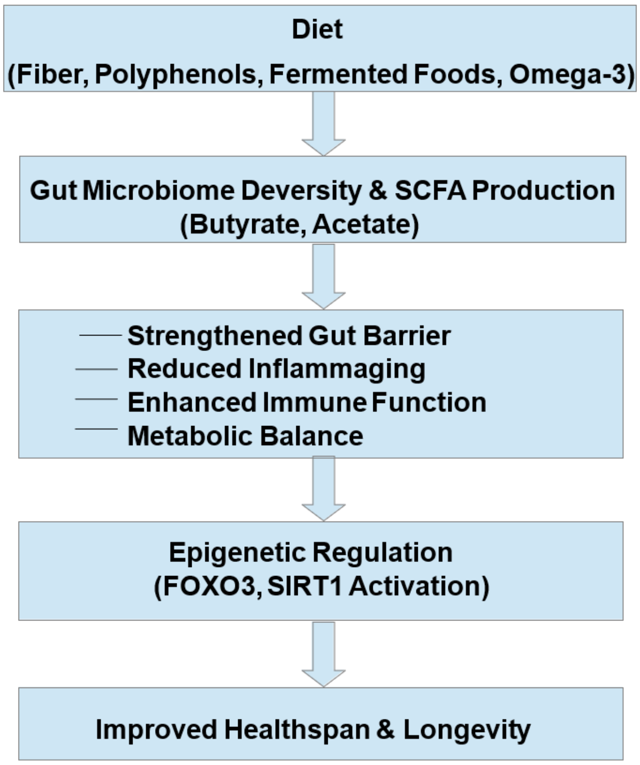

Figure 1: The Interplay Between Diet, Gut Microbiome and Longevity. This flowchart represents the mechanistic connection between diet, gut microbiome diversity and longevity. Dietary factors, such as fiber, polyphenols, fermented foods and omega-3 fatty acids, may affect both gut microbiome composition and functions. A well-balanced microbiome boosts Short-Chain Fatty Acid (SCFA) production, mainly butyrate and acetate, which support gut homeostasis. They also help maintain the integrity of the gut mucosal barrier, reduce chronic, low-grade inflammatory responses ("inflammaging"), strengthen immunity responses and balance metabolism. SCFAs support immunity, reduce disease risk and influence gene activity by activating FOXO3 (Forkhead Box O3) and SIRT1 (Sirtuin 1), which boost stress resistance and lower inflammation. Ultimately, the integration of these mechanisms enhances immune resilience, reduces disease susceptibility and extends healthspan, highlighting the critical role of gut microbiome modulation in aging.

Taken together, while the concept of a singular "longevity diet" may be overly reductive, the evidence supporting a microbiome-targeted, cognition-preserving dietary approach is increasingly robust. Promoting such dietary patterns across the lifespan may not only enhance systemic metabolic resilience but also protect the structural and functional integrity of the aging brain-positioning the gut microbiome as a central modifiable determinant in mitigating age-related cognitive decline.

Challenges & Future Directions

Dietary interventions aimed at the microbiome are difficult to implement since the microbiota composition changes during life. Indeed, diet, environment, medication and lifestyle appear to be constantly affecting the generally orderly pattern of microbiome development from infancy to old age. The microbiome during early life is critical for immune system development and maternal nutrition and breastfeeding are especially important [121,122]. Dietary patterns in general have a more particular effect on the microbiomes of adolescents and adults. In aged individuals, where increased inflammation and NDs are associated with dysbiosis, intervention efforts should be tailored to age-related changes in the microbiome to improve health at various phases of life.

Dietary interventions should vary in accordance with timing and microbiological needs throughout a person's life. Pre-and probiotics, for example, may assist in increasing colonization by "good" bacteria in infants, while fiber-and polyphenol-rich diets may benefit adults by increasing gut microbiota diversity and thereby aiding in metabolic health. Restoring beneficial bacteria to the gut of older adults through fermented foods, resistant starches and synbiotics may reduce age-related gut imbalances and inflammation. A tailored strategy will thus necessitate the use of additional specific biomarkers to track changes in the microbiome as a result of dietary changes. Dietary approaches should be tailored to each life stage. For example, prebiotics and probiotics may help build beneficial bacteria in early life, while fiber-and polyphenol-rich foods support microbial diversity and metabolic health in adults. In older adults, fermented foods, resistant starches and specific synbiotics can help restore healthy microbes and reduce age-related gut imbalances and inflammation. For optimal outcomes, tailored nutrition programs require reliable biomarkers to accurately assess microbiota responses to dietary interventions.

A recent study examined how diet and microbiome interact by analyzing stool, focusing on dietary components and microbial metabolites [123,124]. Metabolomic analysis of stool and other samples helps us understand how the gut processes food and how diet affects microbial changes [125,126]. They most likely find a microbial profile that is important for longevity, metabolic health and/or disease resistance. Feeding analysis, microbiome sequencing and metabolomics appear to have the potential to lead to the development of tailored diets. To improve longevity, we need to combine microbiome research, nutrition and bioinformatics. Long-term studies on diet changes and their effects on gut microbiomes can help identify links to health outcomes. AI-based methods could create personalized dietary recommendations from stool microbiome analysis, aiming to enhance lifespan and health. Additionally, studying how climate change affects food quality and availability is important, as it may impact global microbiomes and health [127,128]. At the same time, it is important to recognize that a healthy and diverse gut microbiome typically promotes healthy aging; however, Gram-negative bacteria that may be present in probiotics or fecal microbiota may release *Lipopolysaccharide* (LPS), which is an endotoxin that activates TLR4-NF-κB signaling and inhibits expression and/or activity of sirtuin 1 (SIRT1) [129-132]. LPS does not directly inhibit SIRT1 enzymatically, but rather LPS downregulates SIRT1 via pro-inflammatory pathways, thereby affecting epigenetic regulation and enhancing "inflammaging." [133] Given SIRT1's central role in promoting chromatin remodeling and gene expression associated with longevity, increased LPS levels when presented with dysbiotic or aged microbiota can downregulate important pathways for healthy aging [134,135]. This suggests that we need to reach a balance between microbial diversity and endotoxin burden when devising therapeutics with probiotics or fecal microbiota.

Building on this, correlating specific diets to healthy gut bacteria or isolating specific dietary components to build pharmacological compounds that can potentially expand longevity is a promising field of research. Globally, individuals adhere to specific diets due to diverse factors, including health conditions, economic constraints and cultural practices. That being said, a pharmacological approach dealing with specific dietary components may function as an option to improve gut health in the face of indifference in dietary food choices. This option will provide easier access to critical bioactive components that are not available through certain diets. These approaches, if developed, will be critical to making the microbiome's benefits more widely available to the general public. Dietary changes that target the microbiome, combined with non-invasive tests on stool sample material and modern pharmaceutical methodologies, could lead to new approaches for promoting gut health and mitigating age-related diseases, thereby improving quality of life in various age groups.

Conclusion

The gut microbiota influences nutrition, metabolism, immune function and epigenetic regulation, all of which contribute to longevity and aging. A healthy and diverse microbiota can enhance the nutritional benefits of fiber-and polyphenol-rich diets by generating bioactive metabolites such as SCFAs. These metabolites play a critical role in strengthening the intestinal barrier and reducing inflammation-both key determinants of aging. Conversely, dysbiosis resulting from diets high in processed foods may accelerate aging and increase susceptibility to age-related diseases. While probiotics and fecal microbiota transplantation hold therapeutic potential, dietary intervention remains the most practical and sustainable strategy to support healthy aging. Future research should prioritize elucidating causative mechanisms and advancing personalized dietary approaches to optimize the microbiome's impact on healthspan and quality of life.

Conflict of Interest

The authors do not have anything to declare.

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Author Contribution

Conceptualization and supervision: S. K. C.; Formal analysis: S. K. C.; Original draft preparation: S. K. C.; Writing-review and editing: S. K. C. and D. C.; Project administration: S. K. C.; Funding acquisition: S. K. C.

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