Received: 12 April 2024 | Accepted: 30 May 2024

DOI: 10.1002/agm2.12336

Aging Medicine Open Access WILEY

REVIEW ARTICLE

Gut microbiota in centenarians: A potential metabolic and aging regulator in the study of extreme longevity

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Funding information
COOSALUD EPS

Abstract

Centenarians, those aged 100 years or older, are considered the most successful biological aging model in humans. This population is commonly characterized by a low prevalence of chronic diseases, with favorable maintenance of functionality and independence, thus determining a health phenotype of successful aging. There are many factors usually associated with extreme longevity: genetics, lifestyles, diet, among others. However, it is most likely a multifactorial condition where protective factors contribute individually to some extent. The gut microbiota (GM) has emerged as a potential factor associated with the establishment of a favorable health phenotype that allows for extreme longevity, as seen in centenarians. To understand the possible impact generated by the GM, its changes, and the probable causes for successful aging, the aim of this review was to synthesize evidence on the role of the GM as a potential protective factor for achieving extreme longevity, using its relationship with centenarians.

KEYWORDS
aging, centenarians, geroscience, gut, healthy aging, longevity

1 | THE IMPORTANCE OF STUDYING AGING AND CENTENARIANS

The aging of global population is an unprecedented phenomenon that will cause a radical shift in the conception and approach to human health and disease. According to data from the World Health Organization (WHO), it is estimated that by the year 2050, the proportion of people over 60 years old will account for 22% of the total global population (around 2.1 billion), with 80% of them living in low- and middle-income countries.[1] Additionally, the population over 80 years old will be close to 430 million.[1] Based on the current aging trend, which is associated with the rise of age-related chronic diseases,[2] the global disease burden and healthcare costs they produce, would be unsustainable for many healthcare systems worldwide.[3,4] In an attempt to resolve this, the United Nations (UN) declared the period from 2021 to 2030 as the Decade of Healthy Aging,[5] aims to optimize opportunities for maintaining and improving the well-being, functional capacity, physical and mental health, and quality of life of the aging population.

Diverse factors have been associated with healthy or unhealthy aging such as demographic factors[6–9]; prosociality level,[10] physical and organic health status,[11,12] mental health,[13] lifestyle factors,[14,15] and genetics.[16–18] This converges in the concept of biological aging (BA), defined as the set of processes that cause organ deterioration over time.[19] BA depends on the complex interaction of these factors,[20] which can lead to a heterogeneous aging process across

multiple organic systems,[12] and correlate with a specific survival time and health or disease phenotype even in advanced ages.[12]

To deeply understand the mechanisms associated with aging and to identify potential targets for intervention to control or delay BA and the onset of diseases, it is necessary to study successful BA models. These models reflect phenotypes that are resistant to external stress factors with a favorable organic response.[21,22] Centenarians, individuals with a chronological age (CA; defined as the number of years an individual has lived) equal to or greater than 100 years, constitute one such model of successful aging.[21] The proportion of centenarians globally increases significantly and quietly.[23] Some sources claim that there are currently at least 500,000 centenarians in the world, with expectations that this number will increase to millions by the year 2100.[23] This group is essentially characterized by reaching this CA with adequate adaptation to BA,[24] represented by a relatively healthy morbidity profile (considering the time of exposure to external stressors throughout their lives), as few are polymorbid and maintain proper functional capacity.[25–27] What causes these individuals to have a more favorable aging phenotype, placing them at the extreme end of the Gaussian bell curve of aging?

Currently, there is a significant knowledge gap from the translational perspective due to the evolutionary and exhaustive nature of aging research, which requires robust and reproducible omics studies on populations (specially in centenarians).[28] These studies would aid in understanding precisely how modifiable and nonmodifiable factors impact the organic evolution of centenarians. Cellular senescence, epigenetic clocks, and alterations in stem cells,[29] are some of the cellular and molecular processes that could theoretically reflect cellular proteodynamics,[30] adaptation to aging,[31] and the development of health phenotypes and prognosis during longevity.[32] Having specific data on these mechanisms could facilitate the identification of aging biomarkers for cells, tissues, organs, or diseases,[33] and predict the onset of age-related chronic diseases. However, there are not enough, studies to corroborate these hypotheses based on centenarians as a model of successful aging. Therefore, evidence regarding possible interventions to delay aging and prevent the onset of age-related chronic diseases into extreme ages remains weak and speculative.

The gut microbiota (GM) has been described as a biological and metabolic regulator of various organs and diseases.[34] Age and diet, determinants in aging, are two factors directly related to the establishment and modification of the composition of the GM.[35] To date, little discussion has taken place regarding the specific changes that occur in the long-lived population, which allow the establishment of an antioxidant system with characteristics similar to those of a young population, as a result of successful evolutionary adaptation.[36] Although the specific mechanisms are unknown, this may possibly be one of the strongest reasons influencing life expectancy and healthy lifespan during aging. To understand the possible impact generated by the GM, its changes, and the probable causes for successful aging, the aim of this review was to synthesize evidence on the role of the GM as a potential protective factor for achieving extreme longevity, using its relationship with centenarians.

2 | DETERMINANTS AND PROTECTIVE FACTORS FOR HEALTHY AGING AND EXTREME HUMAN LONGEVITY: MATTER MUCH OR LITTLE?

While nonmodifiable factors such as gender and CA significantly impact human aging and life expectancy,[37] modifiable factors play a crucial role throughout life, maintaining or altering health phenotype.[6,11,13] Consequently, these factors influence healthy lifespan, type of aging, and overall quality of life. For instance, there is a predisposition for women to be biologically more resistant and resilient to BA compared to men (possibly due to possessing two X chromosomes, which provides a degree of protection against mutations in this chromosome).[37,38] This is clearly observed in centenarian cohorts where, in addition to be predominant, women tend to age more successfully.[8,39,40] However, there is also evidence that has identified how clinical, behavioral, and socioeconomic variables during childhood and adolescence are associated with a higher risk of premature death.[6,20] Therefore, there is no single answer. It is necessary to explore clusters from biological, demographic, social, and clinical data to comprehend and address questions about extreme longevity. To accomplish this task, we must ask ourselves: What are the most important factors to consider during the study of healthy aging and extreme longevity, and how much information do centenarians provide for understanding these mechanisms?

Previously, the urgent need to thoroughly study aging as a global health priority has been emphasized, considering the challenges, gaps, and benefits of developing evidence-based interventions[41,42] that can be applied to long-lived population. The absence of randomized controlled trials in centenarian populations focused on the prevention, control, and treatment of age-related chronic diseases[43,44] as well as massive exclusive centenarian cohorts with long-term follow-up that allow for a deep understanding of the biological, social, behavioral, and clinical changes experienced by this specific population group,[45] are some examples of the current gaps in evidence regarding one of the most successful aging models. Particularly, the lack of evidence in both clinical and translational research in centenarians hampers the design and implementation of evidence-based specific strategies due to discrepancies in decision-making[46,47] making it difficult to promote their health outcomes and disability-free life expectancy. To gain a deeper understanding of the considerations that need to be discussed before studying centenarians, we believe there are concepts that must be understood to assess the heterogeneity and validity of original data from different parts of the world. This is due to the demographic, cultural, social, and genetic diversity across different regions worldwide.

3 | THE GM AS A DRIVER OF EXTREME LONGEVITY? EVIDENCE IN CENTENARIANS

The GM is a malleable ecosystem capable of adapting its functional and phylogenetic profile to environmental, dietary, lifestyle,

TABLE 1 Identified bacteria in GM patterns in centenarians, related biological modifications, and association with the development of specific health phenotypes.

Bacteria	Microbiological characteristics	Expression in centenarians	Biological, molecular, or physiological modifications	Possible association with health/disease phenotypes
Akkermansia muciniphila (36)	Gram-negative bacteria, anaerobic with an oval shape, belonging to the phylum *Verrucomicrobia* (67)	↑ (67)	When degrading mucin, it produces acetate and propionate, serving as substrates for other bacteria and the host (68,69)	Protects against inflammatory bowel disease, metabolic syndromes, obesity, and diabetes (67)
Christensenella minuta	Gram-negative bacteria strictly anaerobic, nonspore-forming, nonmotile, negative for catalase, oxidase, urease, and indole produce (70)	↑ (36)	In glucose fermentation, it produces acetic and butyric acid. (70) It alters the microbial ecosystem, reducing opportunistic pathogens and increasing commensal bacteria by generating competition for nutrients (71)	Protects against obesity, metabolic diseases, intestinal diseases, and glycemic levels (71)
Lactobacillus johnsonii	Gram-positive bacteria, facultative anaerobe, nonspore-forming, rod-shaped, and belonging to the phylum *Firmicutes* (72)	↑ (36,66)	Specifically increases the proportion of intestinal macrophages and IL-10 secretion (73)	Prevention of colitis, antiinflammatory effect (73)
Lactobacillus oris	Gram-positive bacteria, facultative anaerobe, nonspore-forming, rod-shaped, and belonging to the phylum *Firmicutes* (72)	↑ (36,66)	Reduces lipids by inhibiting the production of the enzyme 3-hydroxy-3-methylglutaryl CoA reductase (74)	Prevention of liver diseases (74)
Lactobacillus gasseri	Gram-positive bacteria, facultative anaerobe, nonspore-forming, rod-shaped, and belonging to the phylum *Firmicutes* (72)	↑ (36,66)	Induces BDNF expression, suppresses NF-κB activation, and intestinal microbiota dysbiosis (75)	Prevention of psychiatric disorders (75)
Lactobacillus plantarum	Gram-positive bacteria, facultative anaerobe, nonspore-forming, rod-shaped, and belonging to the phylum *Firmicutes* (72)	↑ (36,66)	Displays antioxidant activity through the elimination rate of 1,1-diphenyl-2-picrylhydrazyl, reducing activities of L-cysteine equivalent, elimination rates of hydroxyl free radicals, rates of ferrous ion chelation, rates of superoxide anion elimination, and inhibition of lipid peroxidation (36)	Promotes longevity, possesses an antitumor effect, and is associated with immune system remodeling (36)
Megamonas	Gram-negative bacteria, nonspore-forming, pleomorphic in shape, ranging from short coccobacilli to long and irregular rod-shaped cells (76)	↓ (77)	Responsible for hexitol fermentation to lactic acid, formic acid, ethanol, and acetic acid, precursor metabolites, and energy; degradation of myo-inositol; guanosine nucleotide degradation; promotes adipogenesis and cholesterol formation (78,79)	Is related to the risk of metabolic diseases such as nonalcoholic fatty liver (79)
Roseburia intestinalis	Anaerobic gram-positive bacteria, with a slightly curved and flagellated rod-shaped morphology, degrades and utilizes oligofructose as the sole source of energy when acetate is present in its environment (80)	↑ (77)	Produces butyrate through the enzyme Butyryl-CoA: acetate CoA transferase, ferments xylan and β-mannan, produces flagellin, and regulates barrier homeostasis, immune cells, and cytokine release (80)	Prevents metabolic diseases and has an anti-inflammatory effect (80)

TABLE 1 (Continued)

Bacteria	Microbiological characteristics	Expression in centenarians	Biological, molecular, or physiological modifications	Possible association with health/disease phenotypes
Faecalibacterium	Strictly anaerobic gram-positive bacteria, bacillus-shaped, nonmotile, and nonspore-forming (81)	↓ (77)	Its final products from glucose fermentation are formate, D-lactate, and butyrate; it can ferment pectin and inulin and transform avenanthramides into dihydroavenanthramides (81)	Possesses antioxidant and anti-inflammatory effects, a decrease in *Faecalibacterium* is associated with inflammatory bowel diseases, irritable bowel syndrome, obesity, liver disorders, metabolic conditions, cancer, neurological conditions, and dermatitis (81)
Bifidobacterium adolescente	Strict anaerobic gram-positive bacteria, typically residing in the GM (82)	↑ (77)	Has the ability to transform monosodium glutamate precursor into GABA (83)	Prevents anxiety and depression disorders (83)

pharmacological, and stress-related changes. This functional plasticity optimizes the metabolic and immunological performance of the host in response to physiological and environmental dynamics, preserving homeostasis and health.[48] It is estimated that around 1000 different microbial species constitute the human GM. Among these, the predominant species are *Firmicutes* and *Bacteroidetes*, followed by *Actinobacteria*, *Verrucomicrobia*, and *Proteobacteria*.[49,50] Variations in human microbiota colonization findings are attributed to factors such as geography, genetics, diet, antibiotic consumption, and gastrointestinal diseases.[51] Moreover, it has been demonstrated that exposure to antibiotics during pregnancy, cesarean section birth, postnatal antibiotic administration, and formula feeding can all disrupt early intestinal microecology, and these factors have been linked to the risk of disease in later life.[52,53]

Once the GM is structured, it forms an interconnected microbial community that intimately relates to various organic functions, including both digestion and nutrient absorption, regulation of immune function, and modulation of physiological stress response. This symbiotic relationship grants the human being the status of a "meta-organism," making it interdependent on the characteristics of the microbial community. Based on the impact exerted by the GM (with its primary commensal function) on various organic functions, this agent has been considered as a metabolic, endocrine, and immunological organ. This recognition is due to its evolution and ability to control low-grade chronic inflammatory responses, inherent GM dynamics.[54,55] Thus, the sterolbiome, defined as the genetic potential of the GM to produce endocrine molecules from both endogenous and exogenous steroids in mammals, is formed. Over time, due to exposure to external factors and adaptation to aging, diverse reactions triggered changes in the metabolism of different tissues.[56] For this reason, the assessment and recognition of the GM and its diversity as an agent associated with aging are essential during the study of longevity and centenarians (Table 1). This association is closely related to regulatory mechanisms governing the cellular and immunological adaptation of human beings throughout their lives.

Chronic low-grade inflammation associated with aging, known as "inflammaging," has a significant impact on the GM, triggering irregular variations that disrupt the physiological and metabolic mechanisms of this organ. Persistent inflammation leads to higher levels of aerobic conditions and an imbalance in the production of reactive oxygen species, which inactivates the reproduction and survival of anaerobes such as *Firmicutes* (associated with better health phenotypes) and favors the colonization of facultative aerobes, often observed in individuals experiencing unhealthy aging. These negatively impacting microorganisms, known as "pathobionts," such as *Enterobacteriaceae*, *Enterococcaceae*, *Staphylococcaceae*, create a mutualistic symbiosis that perpetuates inflammation.[48,57] Therefore, studying inflammaging, comorbidities, GM, and health profiles in centenarians has the potential to answer questions about the possible association between an individual's adaptation and favorable cellular response with a microbiota exhibiting specific characteristics in a population with unique environmental features (Figure 1).

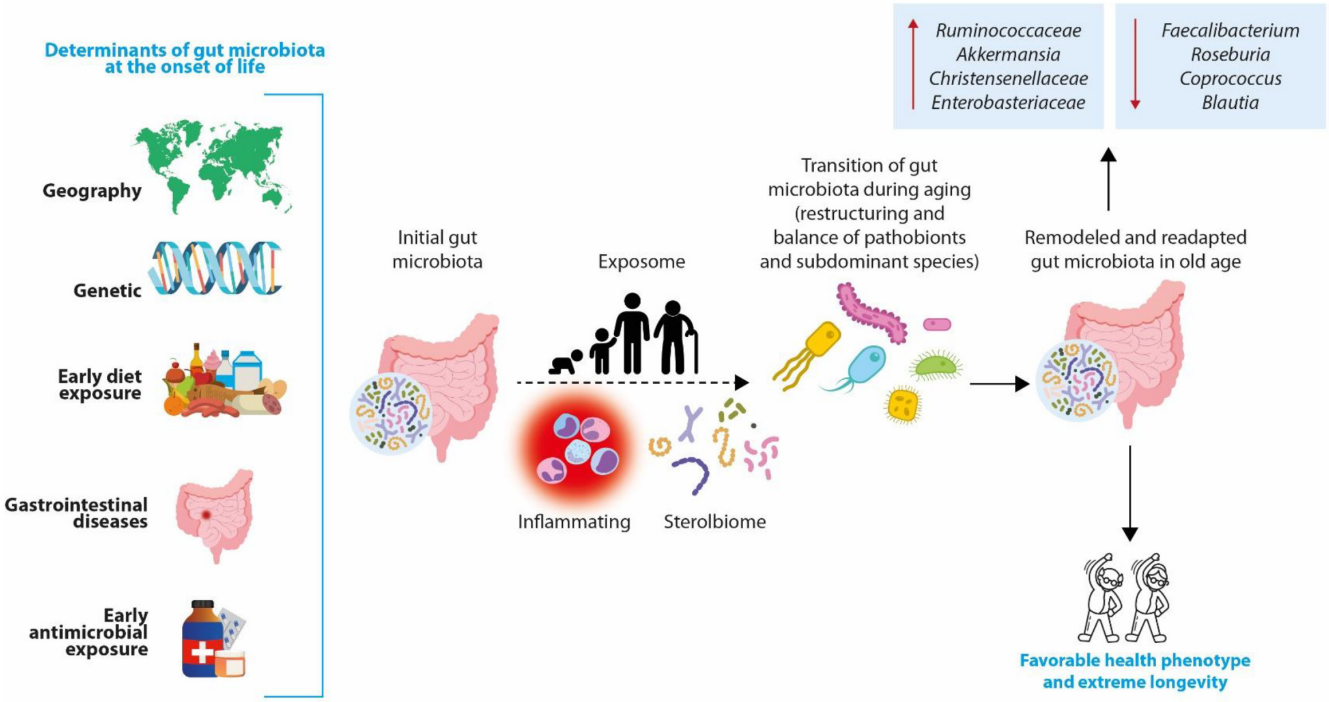

FIGURE 1 Evolution of the GM throughout life, and factors associated with the transition, remodeling, and adaptation of the GM during aging leading to a favorable health phenotype and extreme longevity.

This research can provide valuable evidence on how this protective phenomenon against inflammaging occurs.

A microbiota composed of a dominant symbiotic bacterial community (such as *Bacteroidaceae* or *Ruminococcaceae*) leads to a loss of diversity and abundance with age. In extreme longevity, such as in centenarians, this readaptation is counteracted by an increase in subdominant species related to aging (for example, *Bifidobacterium* and *Akkermansia*), which, depending on colonization characteristics, can contribute to a specific state of health. Thus, the transition of the GM during aging, involving the loss of certain components, is compensated by a new GM with potential pathobionts (a crucial element to study as a possible target for intervention or prediction of aging). This tolerance property in restructuring can be utilized in researching therapeutic targets for senolytics, aiming to repopulate the GM during aging and attempting to delay or regulate inflammaging and BA.

A valuable piece of information to understand this phenomenon is, at extreme ages, that it has been found that the restructuring of human GM acquires properties typical of the microbiota of ancestral communities.[58,59] This comparison revealed specific GM adaptations to the respective subsistence strategies, including higher diversity and enrichment in microorganisms generally considered as pathobionts (e.g., *Prevotella*, *Treponema*, *Bacteroidetes*, and *Clostridiales*) in the GM from ancestral populations. Interestingly, this finding correlates with results from GM in rural communities, which possess better co-evolutionary adaptations.[60] This is a special consideration during the analysis and comparison of the structure and characteristics of GM among areas with different geographical and environmental features.

Findings derived from cohorts studied in blue zones where there is a high rate of long-lived population, such as in Italy or China, have shown that their GM is enriched with *Ruminococcaceae*, *Akkermansia*, and *Christensenellaceae*, which have been classified as potentially beneficial bacteria. These bacteria have been linked to body mass index, immunomodulation, and healthy homeostasis.[35,51] Importantly, a decrease in *Faecalibacterium*, *Roseburia*, *Coprococcus*, *Blautia*, and an increase in *Enterobacteriaceae* were observed in subjects aged 90 and 100 years, resembling the age-related microbiota features found in Italian centenarians but with some differences from Chinese centenarians.[61]

Remarkably is the distinct metabolic pattern exhibited by centenarians, associated with the GM. Specific modifications affect glycerophospholipids and sphingolipids, alongside decreased circulating levels of lipid peroxidation markers which manifest in the longevity phenotype observed in Italy. This occurrence results from the profound influence exerted by the longevity process on the structure and composition of the metabolome derived from the human GM. This influence is evidenced by the excretion of certain metabolites, such as phenylacetylglutamine and p-cresol sulfate, observed in the urine of Italian centenarians.[62] In contrast, in other regions such as the United States, evidence of high concentrations of metabolites like isocitrate and taurocholate, products derived from citric acid and bile acid metabolism, respectively, has been associated with a lower likelihood of reaching the age of 80.[63] However, in Bama, China, a documented Blue Zone, centenarians exhibit high levels of fecal short-chain fatty acids and total bile acids,[64] which is contradictory and intriguing to investigate in depth.

So, it is clear that the GM represents a hot topic in studies of healthy aging, considering its impact on various organic axes and the establishment of health and disease phenotypes. In centenarians, there is still limited evidence available due to the extensive diversity of the microorganism community, which can vary based on geographic location, lifestyles, medication, or associated diseases. Nevertheless, understanding the features of microbial signatures in the GM would allow discovering potential novel mechanisms related to the adaptation and physiological response of centenarians, either in favor or against their healthy aging phenotype.[51] This would facilitate the identification of therapeutic targets, possible interventions based on restructuring, recolonization, and control of the microbial community, and serve as a set of biomarkers for healthy aging and health status, predicting the onset and response to certain age-related chronic diseases.[65]

This landscape forces us to consider the GM as a variable of great interest in discovering the novel and unknown mechanisms on the physiology and physiopathology of centenarians. This, because it reflects the adaptation and immunological resilience in the gastrointestinal tract for over 100 years. Few studies have translationally associated the health phenotype of centenarians with the evolution of the GM throughout their lives.[66] There might not even be active prospective cohorts with open-access data revealing information about these characteristics, enabling a deeper understanding of the differences and impact of GM among very long-lived communities. Some of these variables to consider in future studies could be the mode of birth, type, and quality of postnatal breastfeeding, environmental exposure, and hygienic conditions. Therefore, a mixture of approaches, including anthropological, biodemographic, environmental, clinical, social, and translational, is essential to unveil critical and precise data about the relationship between GM, centenarians, and healthy aging.

4 | CONCLUSIONS

Evidence suggests that there are significant changes in the composition of the GM of centenarians, compared to other age groups, which could be associated with specific phenotypes of healthy aging, and be determinants in extreme longevity. However, numerous factors condition the establishment of the GM over time. The origin of the data is limited to certain countries with some blue zones. This field should be extensively studied in regions lacking data and determine the possible specific causal association between genera and species of microorganisms, and extreme longevity.

AUTHOR CONTRIBUTIONS

IDLM contributed to the conception and design of the study. IDLM and LMLM carried out data collection and data cleaning. IDLM, LMLM, and JMA drafted the manuscript. IDLM, LMLM, and JMA critically reviewed the manuscript with suggestions for improvement and revision. All authors read and approved the final version.

FUNDING INFORMATION

The study was supported by Coosalud EPS.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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How to cite this article: Lozada-Martinez ID, Lozada-Martinez LM, Anaya J-M. Gut microbiota in centenarians: A potential metabolic and aging regulator in the study of extreme longevity. *Aging Med*. 2024;7:406-413. doi:10.1002/agm2.12336