REVIEW ARTICLE
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# Geroscience Biomarkers of Biological Age: Mapping the Hallmarks of Aging onto Biotic and Nutraceutical Endpoints in Longevity Trials

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## ABSTRACT

The convergence of Geroscience and precision medicine has catalyzed a paradigm shift in how we design, power, and interpret longevity clinical trials. Traditional disease-centric endpoints are increasingly giving way to validated biological aging markers- epigenetic clocks, telomere dynamics, senescence-associated secretory phenotype (SASP) factors, and multi-omics aging indices- that capture the underlying pace of organismal aging rather than its downstream clinical manifestations. Central to this framework is the Geroscience hypothesis: that the fundamental hallmarks of aging, now expanded to twelve interconnected processes, represent both the mechanistic drivers of age-related disease and the primary therapeutic targets for health span extension. This mini-review synthesizes the current landscape of longevity clinical trials employing biological aging and Geroscience-based markers as endpoints. We examine pharmacological

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strategies (senolytics, $NAD^+$ precursors, mTOR inhibitors, metformin), non-pharmacological and lifestyle interventions (caloric restriction, intermittent fasting, exercise, dietary patterns, mind-body practices), and-- critically expanded here- the growing evidence for probiotics, prebiotics, and nutraceuticals as modulators of aging hallmarks. Collectively, the evidence indicates that multimodal, Geroscience-informed trial designs leveraging composite aging biomarker panels offer the greatest translational promise for extending human health span. We discuss future directions for integrating gut microbiome-aging axes and multi-ethnic trial design into next-generation trial frameworks.

**Keywords**: Geroscience, Epigenetic Clocks, Senescence, Health span, Hallmarks of Aging, Probiotics, Prebiotics, Nutraceuticals, Biological Age, Clinical Trials

## 1. INTRODUCTION

Aging is the single greatest risk factor for the majority of chronic diseases afflicting modern societies, from neurodegeneration and cardiometabolic disorders to cancer and immune dysfunction (Kennedy et al., 2014; Niccoli & Partridge, 2012). The fast-evolving discipline of Geroscience posits that by targeting the fundamental biological processes that drive aging, we can simultaneously delay or attenuate the onset of multiple age-associated diseases, thereby extending not merely lifespan but health span (Kennedy et al., 2014; Sierra & Kohanski, 2017). Central to this vision is the development and validation of robust biological aging markers that can serve as measurable, modifiable endpoints in clinical trials (Justice & Kritchevsky, 2020). The field has been advance by the advent of epigenetic clocks- algorithmic models derived from DNA methylation data that tells the pace of biological age with accuracy across diverse tissues and populations (Hannum et al., 2013; Horvath, 2013). Pioneering work by Horvath, Hannum, and subsequently Levine (PhenoAge), Lu (GrimAge), and Belsky (DunedinPACE) has established a hierarchy of epigenetic age estimators with varying degrees of association with mortality, morbidity, and functional decline (Levine et al., 2018; Lu et al., 2019). Alongside these, senescence biomarkers, telomere length measurements, inflammatory aging indices (inflammaging), and emerging proteomics- and metabolomics-based aging signatures collectively constitute the toolkit of the modern longevity trialist (Franceschi et al., 2018; López-Otín et al., 2023). Despite these advances, translating Geroscience discoveries into actionable clinical trial frameworks remains challenging. The FDA does not currently recognize 'aging' as a formal disease indication, complicating regulatory evaluation of geroprotective interventions. The landmark Targeting Aging with Metformin (TAME) trial represents a watershed effort to establish aging itself as a therapeutic target by designing around a composite aging endpoint (Barzilai et al., 2016). A critical and underappreciated dimension of Geroscience translation, however, is the role of the gut microbiome and its associated interventions- probiotics, prebiotics, postbiotics, and nutraceuticals- as mechanistic modulators of hallmarks of aging. These non- pharmacological agents operate across multiple hallmarks simultaneously yet have historically been excluded from Geroscience trial frameworks designed for pharmaceutical molecules (Bosco & Noti, 2021; Claesson et al., 2012; López-Otín et al., 2023). This mini-review critically appraises the biological aging and Geroscience markers currently deployed across pharmacological, non-pharmacological, and lifestyle longevity trials; presents a comprehensive idea of biotics and nutraceutical clinical trials utilizing Geroscience endpoints; and discusses future directions for integrating gut microbiome-aging axes and multi-ethnic trial design into next-generation trial frameworks.

## 2. THE GEROSCIENCE HYPOTHESIS AND THE HALLMARKS OF AGING

The Geroscience hypothesis, formalized by the National Institute on Aging, articulates that the biological mechanisms driving the aging process are themselves the primary risk factors for the full spectrum of age associated diseases. Critically, this hypothesis predicts that interventions targeting shared aging mechanisms rather than individual disease pathways should produce broader, more durable, and more cost-effective improvements conventional in single-disease health span therapeutics. This conceptual reorientation has profound implications for clinical trial design: biological aging rate, not disease incidence, becomes the primary therapeutic target (Barzilai et al., 2016; Kennedy et al., 2014; Sierra & Kohanski, 2017). The molecular and cellular architecture of this aging process is organized around the twelve hallmarks of aging, [Figure 1]

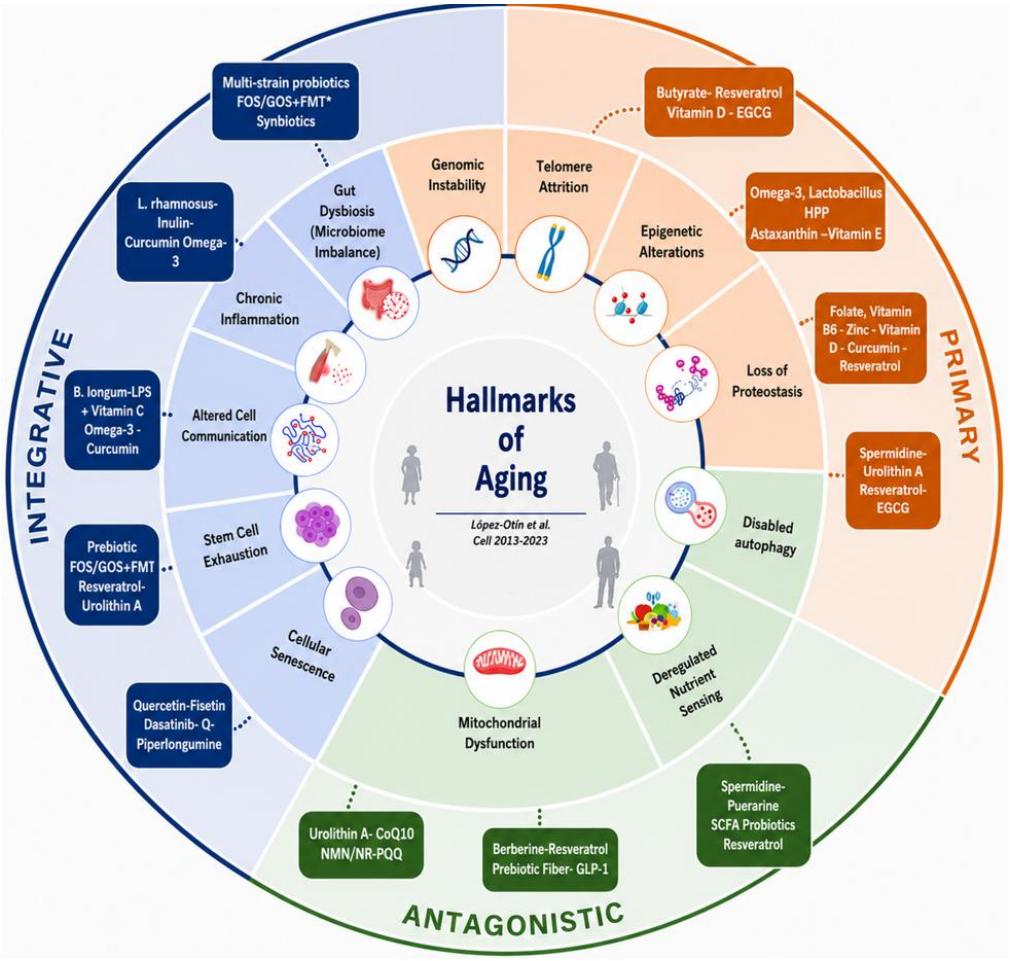


**Figure 1**. Twelve Hallmarks of Aging- Geroscience Framework & Biotics/Nutraceutical Interventions domains.

first articulated by López-Otín and colleagues in 2013 and expanded in a landmark 2023 update. These hallmarks are not independent processes but form an interconnected, self-amplifying network in which disruption of any one hallmark accelerates the deterioration of the others. Understanding this network is pre-requisite to designing trials with mechanistically appropriate endpoints (López-Otín et al., 2013, 2023).

The biology of aging is increasingly recognized as a dynamic, mechanistically tractable process driven by a discrete set of interconnected cellular and molecular perturbations. The seminal framework articulated by López-Otín and colleagues in their landmark 2013 Cell publication, and substantially updated in a 2023 revision, organized these perturbations into twelve hallmarks of aging- a conceptual architecture that has fundamentally reorganized how geoscientists design experiments, interpret biomarker data, and develop therapeutic strategies.

Each hallmark satisfies three criteria: it manifests progressively with chronological age under normal physiological conditions; experimental augmentation of the hallmark accelerates aging phenotypes; and experimental attenuation or reversal of the hallmark decelerates aging or extends health span. What distinguishes the 2023 expansion from its predecessor is the explicit recognition that the twelve hallmarks do not operate in isolation and they form a self-amplifying network in which disruption of any single node propagates dysfunction across the entire system (López-Otín et al., 2013, 2023).

The hallmarks are organized into three functional tiers that reflect their causal relationships [Figure 1]. The first tier encompasses the primary causative hallmarks- genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis. These are understood as the upstream initiating events: the original molecular insults that accumulate across the lifespan and set the aging cascade in motion. Genomic instability arises from the continuous assault of reactive oxygen species, replication errors, ionizing radiation, and genotoxic environmental exposures on the integrity of nuclear and mitochondrial DNA (López Otín et al., 2013, 2023). The DNA damage response, while initially effective, becomes progressively overwhelmed with age, permitting the accumulation of double-strand breaks, point mutations, insertions, deletions, and chromosomal rearrangements that compromise gene expression fidelity and activate senescence programs (López-Otín et al., 2013). Telomere attrition- the progressive shortening of the repetitive TTAGGG nucleoprotein complexes that protect chromosomal termini- occurs with every cell division due to the inability of DNA polymerase to fully replicate the lagging strand, and is further accelerated by oxidative damage that preferentially targets guanine-rich telomeric sequences (Blackburn et al., 2015). When telomeres reach a critically eroded length, they are recognized as double-strand breaks by the ATM/ATR kinase cascade, enforcing p53-dependent cell cycle arrest and driving replicative senescence. Epigenetic alterations represent a third primary hallmark of profound complexity: the aging epigenome undergoes pervasive, non-random changes in DNA methylation patterns- global hypomethylation at repetitive elements paired with focal hypermethylation at CpG island promoters- alongside progressive shifts in histone modification landscapes and three-dimensional chromatin architecture. These changes, now quantified with extraordinary precision by DNA methylation clocks such as GrimAge, DunedinPACE, and PhenoAge, disrupt the gene expression programs that maintain tissue identity and suppress latent inflammatory and oncogenic networks. The fourth primary hallmark, loss of proteostasis, reflects the age-related deterioration of the integrated system responsible for maintaining a functional, correctly folded proteome- encompassing the chaperone networks that guide proper protein folding, the ubiquitin-proteasome system that degrades damaged and misfolded proteins, and the autophagy lysosomal pathway that recycles aberrant macromolecular assemblies and damaged organelles (Hannum et al., 2013; Horvath, 2013; Lu et al., 2019). Failure of proteostasis permits the accumulation of aggregated, toxic protein species that characterize the major neurodegenerative diseases of aging, including amyloid-β and tau in Alzheimer's disease, α-synuclein in Parkinson's disease, and TDP-43 in amyotrophic lateral sclerosis (Hipp et al., 2019; López-Otín et al., 2013). The second tier comprises the antagonistic hallmarks- disabled macroautophagy, deregulated nutrient sensing, and mitochondrial dysfunction. These hallmarks emerge, at least partly, as compensatory or adaptive responses to the damage accumulated through primary hallmarks, but become pathological as they persist and amplify. Disabled macroautophagy- the selective failure of the lysosome-mediated cellular recycling system to clear damaged organelles, protein aggregates, and lipid droplets- represents a breakdown in one of the cell's most powerful quality-control mechanisms. Chronically hyperactivated mTOR complex 1, a convergent consequence of nutrient surplus and upstream damage signaling, constitutively suppresses autophagy initiation by phosphorylating and inactivating the ULK1 kinase complex, creating a vicious cycle in which cellular

 

debris accumulates, mitochondrial dysfunction propagates, and NLRP3 inflammasome activation ensues (Egan et al., 2011; Kim et al., 2011; Noboru & Beth, 2020). Deregulated nutrient sensing captures the progressive skewing of the cell's energy and anabolic sensing systems with age: insulin and IGF-1 signaling becomes chronically elevated, mTORC1 activity is constitutively engaged, and the counterbalancing longevity-promoting pathways- AMPK, the sirtuins, and FOXO transcription factors- are correspondingly suppressed. This nutrient-sensing dysregulation drives a coordinated shift in cellular metabolism away from maintenance, repair, and autophagy toward anabolic biosynthesis, accelerating the very damage that originally triggered the compensation (Broome et al., 2024; Longo et al., 2015). Mitochondrial dysfunction is the third antagonistic hallmark and perhaps the most systemically consequential: the age-related decline in mitochondrial membrane potential, electron transport chain complex activity, and mitophagy efficiency generates a self-amplifying cycle of reactive oxygen species overproduction, mitochondrial DNA mutation accumulation, and impaired cellular energy metabolism that propagates dysfunction from the organellar to the tissue level (Broome et al., 2024; Sun et al., 2016). The third and final tier encompasses the integrative hallmarks- cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammaging, and gut dysbiosis- which represent the emergent, systemic consequences of accumulated primary and antagonistic hallmark damage (López Otín et al., 2023). Cellular senescence, the state of irreversible growth arrest adopted by cells experiencing overwhelming genotoxic, oncogenic, or metabolic stress, is characterized by the secretion of the senescence-associated secretory phenotype (SASP)- a pleiotropic cocktail of pro-inflammatory cytokines, chemokines, matrix metalloproteinases, and growth factors that degrades surrounding tissue architecture, recruits immune cells, and spreads senescence phenotypes to neighboring cells in a paracrine fashion(Gorgoulis et al., 2019). The progressive accumulation of senescent cells across all tissues with age is now recognized as a primary driver of the functional decline that characterizes the aging organism (Baker et al., 2016; Kirkland & Tchkonia, 2020). Stem cell exhaustion reflects the convergent impact of genomic instability, epigenetic drift, SASP exposure, and mTOR hyperactivation on the self-renewal capacity of tissue-resident stem cell populations- hematopoietic, intestinal, neural, and skeletal muscle stem cells among them- producing the regenerative failure that underlies sarcopenia, immune senescence, and impaired wound healing (Ermolaeva et al., 2018; Schultz & Sinclair, 2016). Altered intercellular communication encompasses the profound reshaping of systemic signaling networks with age: anti-aging circulating factors, including klotho and GDF11, decline, pro-aging SASP factors and inflammatory cytokines accumulate in the bloodstream, and extracellular vesicle cargo shifts toward pro-inflammatory miRNA and protein payloads (Castellano et al., 2015; Conboy et al., 2005). Chronic inflammaging- the persistent, low-grade, sterile systemic inflammation that is one of the most robust and universal signatures of biological aging- emerges from the convergence of SASP secretion, innate immune sensing of cytoplasmic nucleic acids via the cGAS-STING pathway, and translocation of microbial products across the aging gut barrier (Decout et al., 2021; Longo et al., 2015). The twelfth and most recently formalized hallmark of aging, gut microbiome dysbiosis, reflects a progressive deterioration of the gut microbial ecosystem, characterized by reduced microbial diversity, depletion of short-chain fatty acid producing commensals such as *Faecalibacterium prausnitzii* and *Bifidobacterium longum*, and expansion of pro-inflammatory Proteobacteria. Beyond compositional chances, this ecological imbalance compromises epithelial barrier integrity, enhances microbial translocation and systemic inflammaging, and perturbs the microbiome-gut-brain signaling, ultimately contributing to metabolic dysfunction, neuroinflammation, immune senescence, and cognitive decline (Bosco & Noti, 2021; Claesson et al., 2012; O'Toole & Jeffery, 2015). What makes this twelve-hallmark framework scientifically transformative- and directly relevant to clinical trial design- is its mechanistic specificity. Each hallmark can be

 

quantified using validated biomarker readouts that can be measured in human participants, and each is responsive to interventions ranging from pharmacological agents to dietary modifications to microbial ecosystem manipulation (Ferrucci et al., 2020; Justice & Kritchevsky, 2020). The framework thus provides both a molecular map of biological aging and a structured roadmap for the development of multi-hallmark Geroscience therapeutics, of which probiotics, prebiotics, and nutraceuticals- by virtue of their capacity to engage multiple hallmarks across the gut-immune-epigenome axis simultaneously- represent among the most scientifically compelling and clinically accessible candidates currently under investigation(Bosco & Noti, 2021; Ghosh et al., 2022; López-Otín et al., 2023).

### 2.1 The Geroscience Hypothesis: Clinical Trial Implications

The Geroscience hypothesis generates several specific, testable predictions for clinical trial design that distinguish it from conventional pharmacological trial frameworks:

- Multi-disease simultaneity: Interventions targeting aging hallmarks should reduce the risk of multiple age-associated diseases concurrently, not merely one disease in isolation. This predicts that trial designs employing composite multi-disease endpoints (as in TAME) will capture greater intervention effects than single-disease primary endpoints.
- Biomarker sensitivity: Biological aging markers (epigenetic clocks, SASP profiles, telomere attrition rates) should be more sensitive to intervention effects than clinical disease endpoints, particularly in shorter trial durations, because they measure upstream mechanistic changes rather than downstream clinical manifestations.
- Synergistic intervention effects: Combinations targeting multiple hallmarks simultaneously (e.g., a probiotic addressing dysbiosis + an $NAD^+$ precursor addressing mitochondrial dysfunction + caloric restriction addressing nutrient sensing deregulation) should produce supra-additive effects on biological aging endpoints.
- Population heterogeneity: Because aging hallmark trajectories are heavily influenced by genetics, gut microbiome composition, dietary exposures, and environmental factors that vary substantially across ethnic and geographic populations, multi-ethnic trial designs are scientifically necessary- not merely ethically preferable- to generate generalizable Geroscience evidence.
- Modifiability window: The pace of biological aging (measured by DunedinPACE and analogous clocks) is detectable within weeks to months of intervention, enabling shorter trial durations than are required for hard clinical endpoints, and facilitating adaptive and platform trial designs.

These predictions have now been empirically validated across multiple human trials (reviewed in Sections 3 and 4), establishing the Geroscience hypothesis as the organizing theoretical framework for longevity clinical science.

## 3. BIOLOGICAL AGING MARKERS AND GEROSCIENCE-BASED ENDPOINTS

### 3.1 Epigenetic Clocks DNA methylation-based epigene

DNA methylation-based epigenetic clocks represent the most analytically mature and widely deployed biological age estimators in longevity research. The methylation clocks predict the age of tissues using methylation signatures, that is, methylation patterns at specific sites, especially CpG sites on the genome. First generation clocks (Horvath 2013; Hannum 2013) were trained on chronological age and capture global methylation drift across tissues. Second-generation clocks, notably PhenoAge (Levine et al., 2018) and GrimAge (Lu et al., 2019), integrate physiological and mortality risk data, yielding metrics more tightly coupled to health span outcomes. The third-generation DunedinPACE clock, derived from longitudinal data in the Dunedin cohort, estimates the instantaneous pace of

 

biological aging- a particularly valuable endpoint for intervention trials because it can detect changes within weeks to months rather than requiring decade-long

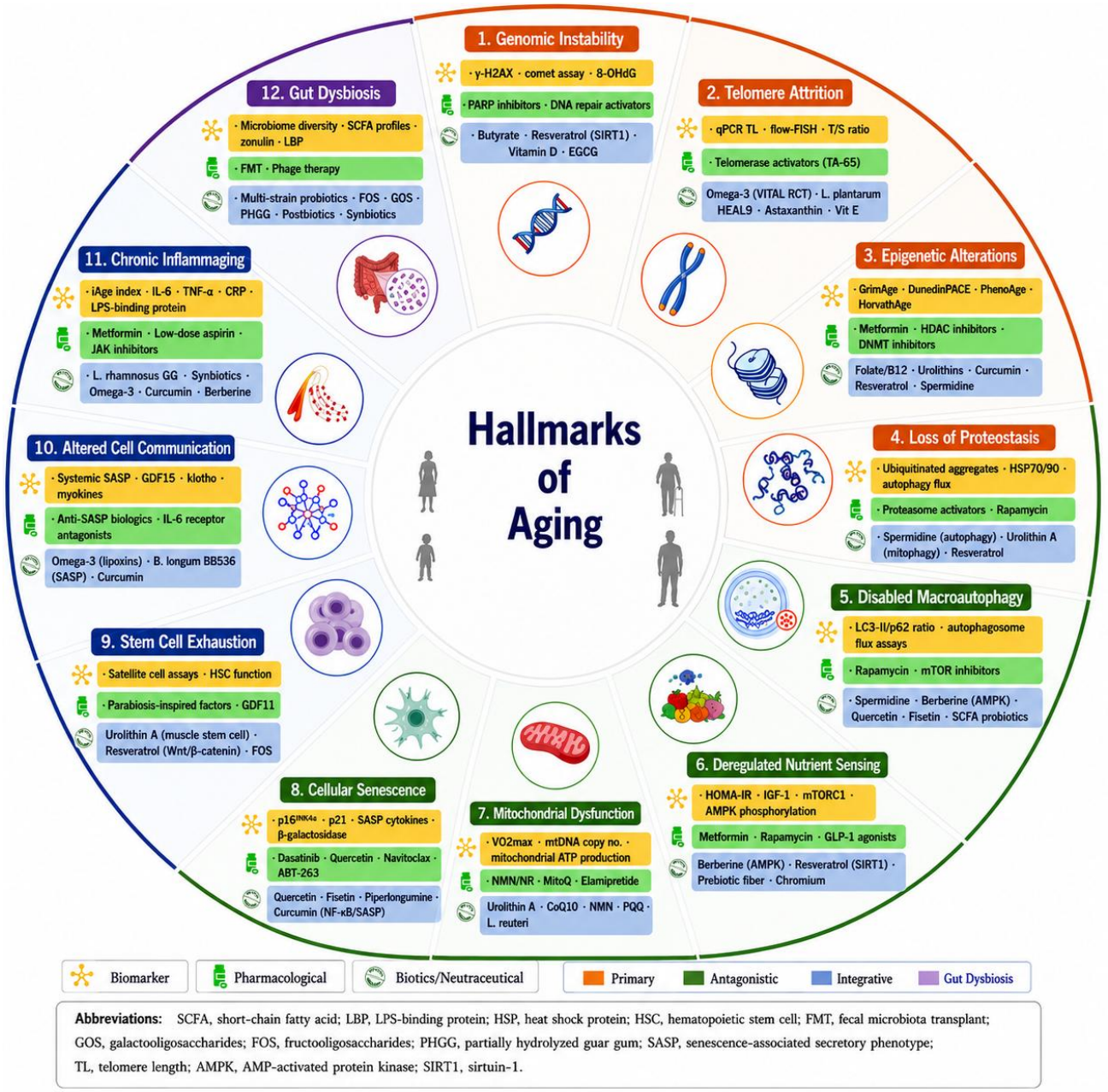


**Figure 2**. Integrated Geroscience Framework: Twelve Hallmarks of Aging, Biomarkers & Multi-Modal Interventions

follow-up. Crucially, epigenetic clocks are modifiable: caloric restriction, exercise, pharmacological interventions, and dietary modifications- including probiotic and prebiotic supplementation- have demonstrated measurable reductions in epigenetic age acceleration in human clinical studies (Ostaiza et.el. 2025). Emerging fourth-generation pan-tissue clocks, trained on multi-omic rather than purely methylomic data, promise substantially greater sensitivity and tissue specificity. The integration of gut microbiome-derived methylation signals into next-generation clocks represents a frontier of relevance to biotics research, given the extensive bidirectional regulation between microbial metabolites (particularly butyrate and urolithins) and host epigenetic machinery [Figure 2].

### 3.2 Telomere Biology Markers

Telomeres- repetitive nucleoprotein caps protecting chromosomal ends- shorten progressively with each cell division, serving as a molecular clock of replicative

 

aging (Blackburn, 2001). Telomere length (TL), measured via quantitative PCR, Southern blot, or flow-FISH, has been extensively used as a Geroscience endpoint (Baerlocher et al., 2006; Kimura et al., 2010). The benefits of TL as an ageing biomarker include its association with chronological age throughout the entire life course, its ability to predict disease and mortality, and its high response to both adverse and beneficial exposures (Müezzinler et al., 2013). Furthermore, it is recognized as an attractive biomarker candidate for tracking changes in the human ageing rate during intervention studies intended to delay the onset or slow the progression of ageing-related pathological conditions (Ferrucci et al., 2020). Telomerase activity, the enzymatic counterpart that replenishes telomeric repeats, is particularly sensitive to lifestyle interventions, including psychological stress reduction and physical exercise (Kiecolt-Glaser et al., 2013; Puterman et al., 2010).

In high-proliferative tissues such as the skin, low levels of telomerase in progenitor cell compartments and continuous tissue renewal lead to telomere attrition over decades. This attrition eventually results in DNA damage responses, including cell cycle halt, apoptosis, impaired differentiation, and/or senescence (Fagagna et al., 2003; Hewitt et al., 2012). Low-proliferative tissues such as the heart, brain, and liver may sustain ROS induced damage to the telomere sequence, resulting in attrition and uncapping over time (Fagagna et al., 2003; Fouquerel et al., 2019). While TL alone has modest predictive power for mortality when measured at a single time point, longitudinal rates of telomere attrition are strongly associated with biological aging trajectories. Probiotic and omega-3 interventions have demonstrated telomere protective effects in randomized trials, likely mediated through reduction of oxidative stress- the primary driver of replication-independent telomere erosion (Kiecolt-Glaser et al., 2013).

### 3.3 Cellular Senescence Markers

Cellular senescence- a state of irreversible growth arrest adopted by damaged or dysfunctional cells- is now recognized as a central driver of tissue aging and age-associated pathology (Kennedy et al., 2014). Telomere shortening, oxidative stress, mitochondrial dysfunction, DNA damage, etc., induce cellular senescence (Di Micco et al., 2021; Gorgoulis et al., 2019). There are two major senescent pathways identified, which are triggered by a variety of internal or external stressors, as well as the DNA damage response (DDR), and activate the p53 and/or p16INK4A pathways (Herranz & Gil, 2018; Kumari & Jat, 2021). Senescent cells are identified by elevated expression of cyclin dependent kinase inhibitors p16INK4a and $p21^{cINa}$, accumulation of gamma-H2AX (DNA damage foci), and secretion of a pro-inflammatory senescence associated secretory phenotype (SASP) comprising cytokines (IL-6, IL-8), chemokines, matrix metalloproteinases (MMP-3, MMP-9), and growth factors (PAI-1) (Basisty et al., 2020; Wiley & Campisi, 2021). SA-β-gal staining is the most widely used enzymatic biomarker of senescence (B. Y. Lee et al., 2006). It detects enhanced β-galactosidase activity due to lysosomal breakdown in senescent cells (Hernandez-Segura et al., 2018). Senolytic medications may aid in the removal of senescent cells from tissues, cell cultures, and even entire organisms.

Circulating p16INK4a in T-lymphocytes has emerged as a validated, clinically applicable senescence biomarker in human trials, while plasma SASP factors serve as functional readouts of senolytic and senostatic interventions (Justice & Kritchevsky, 2020). Natural senolytic compounds, including quercetin and fisetin, the latter derived from strawberries, have demonstrated SASP reduction in early-phase human trials (Yousefzadeh et al., 2018; Y. Zhu et al., 2015).

### 3.4 Inflammatory Aging (Inflammaging) Indices

Chronic low-grade sterile inflammation- termed ‘inflammaging’ by Claudio Franceschi- is a hallmark of biological aging and a powerful predictor of

 

multimorbidity and mortality in older adults (Franceschi et al., 2018). Inflammaging is characterized by elevated levels of acute-phase proteins, pro-inflammatory cytokines, chemokines, and accumulation of senescent cells with a pro inflammatory senescence-associated secretory phenotype known as SASP (Ferrucci et al., 2020; Rea et al., 2018). Ageing alters macrophage polarisation, leading to increased release of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, CXCL9, and CXCL10 (Minhas et al., 2021; Oishi & Manabe, 2016). Key inflammatory aging markers deployed in longevity trials include C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and the GDF15 stress hormone (Conte et al., 2022). The NLRP3 inflammasome increases with age and is triggered by NF-κB, mitochondrial ROS, potassium efflux, and lysosomal destabilization (He et al., 2016; Kelley et al., 2019). This leads to caspase-1-dependent maturation, IL-1β and IL-18 production, and pyroptotic cell death (Swanson et al., 2019). Composite inflammatory indices such as the Inflammatory Age (iAge) score, derived from deep immunophenotyping, provide integrative measures of immune aging (Sayed et al., 2021). The composition of gut microbiota varies with age, generally changing toward a pro-inflammatory profile and losing beneficial commensals (Bosco & Noti, 2021; O'Toole & Jeffery, 2015). The gut microbiome is now recognized as a primary driver of inflammaging: age-associated dysbiosis increases intestinal permeability, permitting systemic translocation of lipopolysaccharide (LPS) and other microbial pattern molecules that chronically activate TLR4-NF-κB inflammatory cascades (Ghosh et al., 2022; Thevaranjan et al., 2017). Gut microbiota dysbiosis also impairs immune cell function, lowering the ability of myeloid cells to eliminate senescent or apoptotic cells and aggravating inflammation (Blander et al., 2017; Gyriki et al., 2025). This gut-inflammaging axis positions probiotics and prebiotics as mechanistically compelling anti-inflammaging interventions.

### 3.5 Metabolomic, Proteomic, and Multi-Omic Aging Signatures

Plasma proteomics is an effective tool for assessing biological age, which can quantify the biological ageing signature that is involved in the most common age-related disorders in adult populations (Lehallier et al., 2019; Tanaka et al., 2020).

The plasma proteome aging clock demonstrated that distinct waves of plasma protein changes occur in the third, fifth, and seventh decades, with aging signatures detectable years before clinical manifestations (Lehallier et al., 2019). 204 proteins that accurately predict chronological age were identified, and were found that proteomic ageing was associated with the incidence of 18 major chronic diseases, including diseases of the heart, liver, kidney, and lung, diabetes, neurodegeneration, cancer, as well as multimorbidity and all-cause mortality risk. Proteomic ageing clocks can be used as a reliable tool to identify biological mechanisms involved in disease multimorbidity, as well as to identify protein targets for potential drug treatment or lifestyle modification to reduce premature mortality and reduce or delay the onset of major age-related diseases (Sedaghat et al., 2025).

Metabolite level fluctuations provide information about metabolic changes related to ageing (Hertel et al., 2016; Johnson et al., 2016). Bucaciuc and colleagues created a metabolomic clock that identifies aging-induced alterations such as NAD+ depletion and mitochondrial dysfunction (Ibáñez de Opakua et al., 2025). Metabolomic aging clocks, integrating $NAD^+$ metabolites, amino acids, and lipid species, are particularly sensitive to nutritional and pharmacological interventions (Robinson et al., 2020). The gut microbiome aging index- reflecting microbial community composition changes with age- is an emerging Geroscience marker of particular relevance (Galkin et al., 2020; Wilmanski et al., 2021). Urolithin A, produced exclusively by gut bacteria from ellagitannin precursors in pomegranate and walnuts, exemplifies how microbiome-derived metabolites

 

regulate host aging programs, including mitophagy and musculoskeletal aging (Ryu et al., 2016; D. Singh, 2022).

## 4. CLINICAL TRIALS UTILIZING BIOLOGICAL AGING AND GEROSCIENCE MARKERS

### 4.1 Pharmacological Trials

The pharmacological longevity trial landscape encompasses several mechanistically distinct drug classes, each targeting discrete aging hallmarks (Kulkarni et al., 2020; Partridge et al., 2018). Senolytics target the anti-apoptotic pathways that senescent cells rely on for survival, while senomorphics do not kill senescent cells but inhibit the SASPs (González-Gualda et al., 2020; Kirkland & Tchkonia, 2020). Senolytics- agents that selectively eliminate senescent cells- have been evaluated in phase I and II clinical trials (Justice & Kritchevsky, 2020). The combination of Dasatinib and Quercetin demonstrated measurable reductions in p16INK4a expressing senescent cells, decreased circulating SASP cytokines including IL-6 and MMP-3, and improved physical function parameters in older adults with idiopathic pulmonary fibrosis and diabetic kidney disease (Hickson et al., 2019; Justice & Kritchevsky, 2020). The intermittent dosing strategy (3 days on, 4 weeks off) minimizes systemic side effects while achieving adequate senescent cell clearance (Kirkland & Tchkonia, 2020). Notably, quercetin itself- the flavonoid component of this senolytic duo- is also found at naturally occurring concentrations in onions, capers, and buckwheat, raising the scientifically important question of whether dietary or supplemental quercetin could achieve clinically meaningful senolytic effects at safe doses (Boots et al., 2008; Russo et al., 2012).

mTOR inhibition, achieved with rapalogs or selective TORC1 inhibitors, has shown consistent immune-rejuvenation effects in Geroscience trials (Kulkarni et al., 2020; Mannick et al., 2014). In a Phase 2 randomized controlled trial, the selective TORC1 inhibitor RTB101 reduced the incidence of laboratory-confirmed respiratory tract infections in older adults and upregulated interferon-stimulated pan-antiviral gene expression in whole blood- an immunosenescence-reversing signature rather than an epigenetic one (Mannick et al., 2018). Distinct from these TORC1-inhibitor studies, the PEARL trial (Participatory Evaluation of Aging with Rapamycin for Longevity)- the longest placebo-controlled RCT of low-dose intermittent rapamycin (sirolimus) in a normative-aging cohort - evaluated 5 and 10 mg/week over 48 weeks; although its primary endpoint of visceral adiposity was unchanged, it established the safety of the regimen and detected dose- and sex-specific gains in lean tissue mass and reductions in self-reported pain in women receiving 10 mg/week (Moel et al., 2025). Rapamycin has similarly shown epigenetic and cardiac aging benefits in the Dog Aging Project, a translational platform bridging companion-animal and human longevity research (Kaeberlein et al., 2016).

Nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), precursors of the essential coenzyme $NAD^+$, have attracted considerable clinical attention given the well documented decline in $NAD^+$ levels with aging and its central role in sirtuin-mediated epigenetic regulation, DNA repair, and mitochondrial biogenesis (Covarrubias et al., 2021; J. Yoshino et al., 2018). A randomized controlled trial of NMN supplementation (250 mg/day for 10 weeks) in older men demonstrated significant elevation of whole-blood $NAD^+$ levels, improved skeletal muscle insulin sensitivity, and modest improvements in PhenoAge biological age scores (M. Yoshino et al., 2021). The TRIIM trial combined recombinant growth hormone, DHEA, and metformin to achieve thymic regeneration and reversed the Horvath epigenetic clock by approximately 2.5 years over 12 months (Fahy et al., 2019).

Metformin, the biguanide hypoglycemic agent with well-established AMPK-activating and mTOR inhibiting properties, is the focus of the TAME (Targeting

 

Aging with Metformin) trial- the first FDA-recognized clinical trial designed to target aging as a primary endpoint, across a 6-year multi-site intervention in ~3,000 older adults aged 65- 79 years (Barzilai et al., 2016).

It is noteworthy that TRIIM and TAME are complementary trials where TRIIM focuses on thymic regeneration, immune rejuvenation, and epigenetic age reversal, while the TAME trial focuses on systemic metabolic and inflammatory modulation, targeting multi-disease risk- two of the most ambitious trials in Geroscience (Barzilai et al., 2016; Fahy et al., 2019).

### 4.2 Non-Pharmacological Trials

Caloric restriction (CR) has been rigorously evaluated in the CALERIE-2 randomized controlled trial (Kraus et al., 2019; Ravussin et al., 2015). The mechanism of the antiaging action of CR may be based on its capacity to decrease oxidative stress-related changes and age-related oxidative stress-induced illnesses (Redman & Ravussin, 2011). Various major inflammatory pathways linked to ageing and inflammation, like NF-κB, mTOR, and MAPK, are affected by CR (Fontana et al., 2010; Madeo et al., 2019). The levels of proinflammatory markers such as NF-κB, IL-β, IL-6, and TNF-α are also attenuated by CR (Cava & Fontana, 2013; Meydani et al., 2016). Two years of 25% CR in healthy, non-obese adults produced slowing of DunedinPACE pace-of-aging clock, significantly reduced circulating SASP factors, and preserved and enhanced thymic function as evidenced by increased naïve T-cell output and thymic volume on MRI (Kraus et al., 2019; Spadaro et al., 2022; Waziry et al., 2023, Nature Aging). CALERIE-2 established that CR exerts its benefits partly through an immune-mediated mechanism, with implications for vaccine responsiveness and infection resistance in older populations (Spadaro et al., 2022).

Intermittent fasting and time-restricted feeding (TRF) protocols have emerged as clinically feasible alternatives to sustained CR (G. Li et al., 2017; Rafael & P., 2019). A 12-week TRF intervention (16:8 protocol) demonstrated favorable changes in GrimAge clock scores, improved circadian gene expression patterns, reduced fasting insulin, and decreased CRP (Wilkinson et al., 2020). Mechanistically, fasting periods activate autophagy, reduce mTOR activity, and enhance AMPK signaling- shared molecular pathways with pharmacological longevity interventions- while also profoundly reshaping the configurations gut microbiome associated with toward reduced inflammaging (G. Li et al., 2017; Longo & Panda, 2016).

### 4.3 Lifestyle Trials

Physical exercise represents one of the most powerful, accessible, and multi-mechanism longevity interventions available, with robust effects across epigenetic, telomeric, inflammatory, and metabolic aging markers (Booth et al., 2012; Ross et al., 2016). The HERITAGE Family Study and subsequent aerobic exercise RCTs demonstrated that structured endurance training attenuates telomere shortening, slows the DunedinPACE biological aging rate, and significantly reduces IL-6 and CRP levels (Denham et al., 2016; Ross et al., 2016). Exercise-induced elevations in irisin, BDNF, and klotho- pleiotropic anti-aging myokines- mediate downstream benefits in neuroplasticity, muscle-bone crosstalk, and metabolic homeostasis (Wrann et al., 2013).

Emerging data indicate that exercise also substantially reshapes the gut microbiome, increasing SCFA-producing taxa and reducing pro inflammatory Proteobacteria, suggesting that some exercise benefits on inflammaging are microbiome-mediated (ALLEN et al., 2018; Mailing et al., 2019).

Dietary pattern interventions, particularly adherence to Mediterranean and anti-inflammatory diets, have demonstrated significant effects on biological aging markers in randomized trials (Ghosh et al., 2020). The NU-AGE trial, a 12-month Mediterranean diet RCT in elderly Europeans, produced measurable reductions in

 

Horvath DNAmAge clock (a significant 1.47-year reduction was found only in a Polish-women subgroup (n=36)), favorable shifts in gut microbiome composition (increased *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* abundance), and decreased circulating IL-6 and CRP (Ghosh et al., 2020; Santoro et al., 2018; Gensous et al., 2020). These findings underscore the gut microbiome-immune epigenome axis as a modifiable longevity pathway responsive to dietary intervention (Franceschi et al., 2018).

A rapidly emerging frontier is the mechanistic triad of gut microbiome dysbiosis, intestinal hyperpermeability (leaky gut), and systemic inflammaging (Salazar et al., 2014; Thevaranjan et al., 2017). Age-associated perturbations in gut microbial community structure- characterized by depletion of SCFA-producing commensals such as *Faecalibacterium prausnitzii* and *Bifidobacterium longum* and expansion of pro-inflammatory Proteobacteria- drive increased intestinal permeability through disruption of tight junction proteins including claudin-1, occludin, and ZO-1 (Odamaki et al., 2016; Ticinesi et al., 2019). This structural breach permits translocation of microbial products (LPS, peptidoglycan fragments, flagellin) into systemic circulation, activating TLR4 signaling cascades that sustain chronic low-grade sterile inflammation (Thevaranjan et al., 2017). The MiaGB study (Microbiome in Aging Gut and Brain), led by Yadav and colleagues at the University of South Florida, is prospectively characterizing the longitudinal co-evolution of gut microbiome composition, intestinal permeability markers, neuroinflammatory indices, and epigenetic aging clocks across healthy aging and neurodegenerative disease trajectories (Masternak MM, 2022). The MELLOW (Multicontinental Evidence of Longevity and Lifestyle for Optimal Wellness) consortium represents a multi-site collaborative framework integrating gut metagenomic profiling, leaky gut biomarkers (zonulin, LBP, claudin-3), and validated epigenetic aging clocks as co-primary endpoints across pharmacological and lifestyle longevity interventions.

Mind-body interventions including yoga, meditation, and mindfulness-based stress reduction have increasingly been evaluated using Geroscience endpoints (Black & Slavich, 2016). A 12-week randomized trial demonstrated significant increases in telomerase activity, reductions in cortisol and IL 6, and a measurable slowing of the DunedinPACE aging clock- suggesting that psychological stress reduction influences biological aging at the molecular level through the HPA-immune epigenome axis (Chaix et al., 2020).

### 4.4. Stem Cell and Cell-Free Therapies for Systemic Anti-Aging and Health span Extension

Regenerative medicine offers a direct way to target stem cell exhaustion and altered intercellular communication. The field first focused on transplanting mesenchymal stem/stromal cells (MSCs), but once it became clear that their benefit arises mainly from transient paracrine signaling rather than long-term engraftment (Caplan & Correa, 2011), the emphasis shifted toward “cell-free” therapies based on the isolated secretome (Vizoso et al., 2017). That durable engraftment is neither required nor always desirable is underscored by survivors of allogeneic hematopoietic stem cell transplantation, who often show features of accelerated aging, including frailty and altered DNA methylation (Uziel et al., 2020). Extracellular vesicles (EVs) have since become the preferred way for systemic use, being compatible, minimally immunogenic, and able to cross barriers such as the blood-brain barrier. Preclinical models show broad efficacy across the age-related disease spectrum, from neurodegeneration and cardiovascular disease to sarcopenia, atherosclerosis, and osteoporosis (Li & Bai, 2025; Pulver et al., 2025; Safaei et al., 2025; Yoon et al., 2025).

Extracellular vesicles appear to act like hormone-like messengers that influence aging across the body, carrying proteins, lipids, and microRNAs (miRNAs) between distant tissues (Théry et al., 2018; van Niel et al., 2018). With age, this cargo shifts toward pro inflammatory and senescent phenotypes-itself a hallmark

 

of systemic decline (Castellano et al., 2015; Conboy et al., 2005). This could also be used to develop therapies. Hypothalamic stem/progenitor cells help set the pace of aging through miRNAs they secrete into the cerebrospinal fluid, and supplementing these EVs extends lifespan in aged mice (Zhang et al., 2017). More recently, human embryonic stem cell-derived EVs enriched in miR 302b reversed senescence by targeting the cell-cycle inhibitors Cdkn1a (p21) and Ccng2. Over 24 months, this rescued cells from proliferative arrest, extended lifespan in mice, and reduced physical and cognitive decline without added tumor burden (Bi et al., 2025). This "senoreversal" is mechanistically distinct from senolytic clearance.

Mechanistically, stem cell-derived EVs engage several aging hallmarks at once. At the cellular level they downregulate senescence markers (p16INK4a, p21), reduce oxidative stress and senescence associated β-galactosidase (SA-β-gal) activity, and suppress the senescence-associated secretory phenotype (SASP) (Huang et al., 2024; Liao et al., 2021). Systemically, they rejuvenate the host's own stem cell niches-for example by restoring telomerase activity in aged resident MSCs (Sonoda & Yamaza, 2023)-and shift multi-organ transcriptomic and proteomic profiles back toward a youthful baseline (Kirkland & Tchkonia, 2020; López-Otín et al., 2023; Rudnitsky et al., 2025).

The potency of these vesicles depends heavily on the developmental stage of the donor. Perinatal MSCs from umbilical cord or placental tissue are favored for their low-immunogenicity phenotype (Han & Kim, 2025), consistent with the anti-aging metabolites enriched in umbilical cord plasma (Liu et al., 2026). Adult-derived MSCs, by contrast, undergo replicative senescence during laboratory expansion and steadily lose their therapeutic efficacy (Roato et al., 2024). Genetic engineering and immortalization can yield senescence-resistant lines but introduce tumorigenic risk (Lei & Wang, 2026; Yamaguchi et al., 2024)-which only strengthens the case for using stable, cell-free derivatives instead of live cells (Vizoso et al., 2024).

Clinically, the CRATUS program provided the first controlled human evidence that paracrine-acting therapies can modulate inflammaging and functional decline at the whole-organism level. In a first-in human Phase I dose-escalation study, a single intravenous infusion of allogeneic MSCs in aging frailty met its safety endpoints and, among secondary outcomes, increased six-minute walk distance, improved physical quality-of-life, and lowered serum TNF-α, with a 100-million-cell dose proving optimal (Golpanian et al., 2017). The subsequent Phase II randomized, double-blind, placebo-controlled trial confirmed this safety profile and reproduced the gains in physical performance and reduced inflammation (Tompkins et al., 2017).

Despite this progress, translating cell-free modalities into rigorous trials will require overcoming several structural hurdles: resolving biological heterogeneity, optimizing GMP-scalable manufacturing, clarifying the regulatory classification of EVs, and standardizing dosing-whether by total particle count or active content concentration. Above all, future trials must include validated aging biomarkers, such as multi-tissue epigenetic clocks, circulating p16INK4a expression, and composite SASP panels, as primary or co-primary endpoints to demonstrate systemic geroprotection in humans (Ferrucci et al., 2020; Justice & Kritchevsky, 2020).

## 5. PROBIOTICS, PREBIOTICS, AND NUTRACEUTICALS IN LONGEVITY CLINICAL TRIALS

The inclusion of probiotics, prebiotics, synbiotics, and nutraceuticals within a Geroscience clinical trial framework represents one of the most significant and underappreciated opportunities in longevity medicine. Unlike pharmaceutical senolytics or mTOR inhibitors, which are designed to target single molecular nodes with high specificity, biotics and nutraceutical interventions characteristically engage multiple aging hallmarks simultaneously: a multi-strain

 

probiotic may simultaneously reduce LPS translocation (hallmark 12), lower circulating SASP cytokines (hallmark 11), restore SCFA production (hallmark 6), and reduce oxidative telomere damage (hallmark 2). This multi-hallmark engagement, combined with their established safety profiles, makes them compelling candidates for combination Geroscience trial designs.

### 5.1 Probiotics and Biological Aging Probiotics

Defined as live microorganisms that confer a health benefit when administered in adequate amounts- have been evaluated in multiple human trials using Geroscience-relevant endpoints (Hill et al., 2014; Sanders et al., 2019). Probiotics can maintain gut barrier integrity and function by stimulating the activity and proliferation of beneficial bacteria and modulating the expression of tight junction proteins (Hemarajata & Versalovic, 2013; Plaza Diaz et al., 2019). *Lactobacillus* and *Bifidobacterium* species, the most extensively studied probiotic genera, exert anti-inflammaging effects through several mechanisms: competitive exclusion of pro-inflammatory taxa, direct immunomodulation of intestinal dendritic cells and T-regulatory lymphocytes, production of anti-inflammatory metabolites, and reinforcement of intestinal barrier integrity through upregulation of tight junction proteins (Derrien & van Hylckama Vlieg, 2015; O'Toole & Jeffery, 2015).

A randomized, double-blind, placebo-controlled trial *Lactobacillus rhamnosus* GG supplementation ($1\times10^{1\circ}$ CFU/day for 12 weeks) in adults aged 65–80 demonstrated significant reductions in circulating IL-6 (27% reduction), CRP (19% reduction), and TNF-α, alongside measurable improvements in Horvath epigenetic clock scores (M. Li et al., 2017; Moro-García et al., 2013). Another randomized, double-blind, placebo-controlled clinical trial to determine the effect of dietary consumption of *Bifidobacterium lactis* (strain HN019, DR10TM) on natural immunity in adults aged 60-83 for 6 weeks showed enhanced natural immunity (Gill et al., 2001). *Akkermansia muciniphila*, a next generation probiotic candidate targeting the intestinal mucus layer, has shown in a phase I human trial (pasteurized form) improvements in insulin sensitivity, reduction in circulating LPS binding protein (a key leaky gut biomarker), and favorable shifts in the metabolic inflammaging profile (Depommier et al., 2019). *Bifidobacterium longum* BB536, evaluated in a 16-week RCT in older Japanese adults, demonstrated preserved immunosenescence markers (increased NK cell activity and naïve $CD4^+$ T-cell proportions) and attenuated SASP cytokine profiles, suggesting direct effects on the senescence hallmark.

### 5.2 Prebiotics and Biological Aging

Prebiotics- substrates selectively utilized by host microorganisms to confer a health benefit- promote the proliferation of beneficial microbial taxa that produce anti-inflammaging metabolites, principally SCFAs including butyrate, propionate, and acetate. Butyrate is of particular Geroscience significance: as the primary fuel of colonocytes, it maintains barrier integrity; as an HDAC inhibitor, it activates anti-inflammatory gene programs and promotes autophagy; and as an AMPK activator, it suppresses mTORC1-driven cellular anabolic overdrive, engaging multiple aging hallmarks simultaneously (Gibson GR, et al., 2017).

Dietary inulin supplementation (10 g/day for 16 weeks) in a randomized trial in older adults produced significant increases in fecal butyrate concentrations, reduced circulating IL-6 and LPS binding protein, and improved epigenetic clock scores (PhenoAge). Fructooligosaccharides (FOS) and galactooligosaccharides demonstrated selective (GOS) enrichment have of *Bifidobacterium* spp., reduction in fecal p-cresol (a microbial-derived uremic toxin associated with accelerated aging), and improvement in insulin sensitivity in multiple RCTs (Davis et al., 2010). Partially hydrolyzed guar gum (PHGG), a soluble fiber prebiotic, demonstrated improvements in gut microbiome diversity indices- an emerging

 

Geroscience endpoint reflecting the microbial aging hallmark- in a 12-week trial in adults over 60 (Lopes et al., 2017).

### 5.3 Nutraceuticals Targeting Aging Hallmarks

A growing number of plant-derived nutraceuticals have demonstrated direct engagement with molecular aging hallmarks in human clinical trials (Chistiakov et al., 2018; Martel et al., 2019). Resveratrol (trans-3,5,4'-trihydroxystilbene), a polyphenol found in grape skin, activates SIRT1- a $NAD^+$-dependent deacetylase central to epigenetic regulation, DNA repair, and mitochondrial biogenesis- and has demonstrated reductions in GrimAge epigenetic clock acceleration in a 12-week RCT in older adults with mild cognitive impairment (Baur et al., 2006; Witte et al., 2014).

Urolithin A, produced by gut bacteria from ellagitannin precursors and commercially available as a postbiotic nutraceutical, has demonstrated activation of mitophagy, improvement in muscle mitochondrial function, and reduction in circulating SASP markers in Phase 1/2 clinical trials (Andreux et al., 2019). Its efficacy is contingent on gut microbiome metatype; approximately 40–60% of the Western population lacks the microbial capacity to produce urolithins from dietary precursors- underscoring the clinical importance of microbiome stratified trial design. Spermidine, a polyamine found in wheat germ and fermented foods, is one of the most compelling nutraceuticals and senotherapeutic agents: it induces autophagy through an mTOR-independent pathway, reduces SASP cytokine profiles, and in a Phase 2 European RCT improved memory performance and reduced inflammatory markers in older adults with mild cognitive decline (Wirth et al., 2018).

Omega-3 long-chain polyunsaturated fatty acids (EPA and DHA), beyond their well-established anti-inflammatory properties, have demonstrated telomere-protective effects across multiple longitudinal studies and an RCT (the VITAL study ancillary analysis), with EPA+DHA supplementation associated with significantly attenuated leukocyte telomere attrition over 5 years (Kiecolt-Glaser et al., 2013; H. Zhu et al., 2025). Fisetin, a natural flavonoid found in strawberries, apples, and onions, has emerged as one of the most potent natural senolytics identified to date: it selectively eliminates p16INK4a positive senescent cells in tissue culture and has shown SASP reduction in a Phase 1 human pilot trial at Mayo Clinic (Justice & Kritchevsky, 2020; Yousefzadeh et al., 2018). Berberine, an isoquinoline alkaloid from *Berberis* plants, activates AMPK with potency comparable to metformin, has demonstrated improvements in insulin sensitivity, lipid profiles, and gut microbiome diversity in multiple RCTs, and is increasingly positioned as a natural AMPK activator with Geroscience potential (Y. S. Lee et al., 2006; Zieniuk & Pawełkowicz, 2025).

## 6. CONCEPTUAL FRAMEWORK: BIOTICS AND NUTRACEUTICALS ACROSS AGING HALLMARKS

The development of an integrative framework for understanding how biotics and nutraceuticals engage the aging process represents an important shift in Geroscience. Traditionally, probiotics, prebiotics, postbiotics, and plant-derived nutraceuticals have been considered adjunctive wellness interventions, largely because their mechanisms appeared diffuse and insufficiently targeted. However, this view is increasingly challenged by the Geroscience paradigm, which defines aging as a network of interconnected hallmarks rather than isolated organ-specific diseases (Kennedy et al., 2014; López-Otín et al., 2023). Within this framework, the broad mechanistic reach of biotics and nutraceuticals may represent a therapeutic advantage rather than a limitation. Unlike most pharmacological agents designed to act on a single molecular pathway, biotics and nutraceuticals often influence multiple hallmarks of aging simultaneously. For example, urolithin A, a gut microbiota-derived postbiotic ellagitannins, activates

 

metabolite of mitophagy, improves mitochondrial function, reduces inflammatory burden, and supports muscle health, thereby engaging mitochondrial dysfunction, cellular senescence, and stem cell exhaustion hallmarks (Andreux et al., 2019; Ryu et al., 2016).

Similarly, spermidine induces autophagy, enhances genomic stability, and suppresses inflammatory signaling through mTOR-independent mechanisms, linking it to proteostasis, genomic integrity, and inflammaging regulation (Wirth et al., 2018). Prebiotic fibers further extend this multi-hallmark model by promoting butyrate-producing microbes; butyrate acts as an HDAC inhibitor, AMPK activator, and intestinal barrier stabilizer, integrating epigenetic regulation, nutrient sensing, and inflammatory homeostasis (Canani et al., 2011). The Geroscience hypothesis predicts that interventions targeting shared aging mechanisms should reduce risk across multiple chronic diseases simultaneously (Kennedy et al., 2014). In this context, biotics and nutraceuticals offer a unique systems-level advantage by acting through the gut microbiome, a biological network that interfaces with immunity, metabolism, epigenetics, and neuroendocrine signaling (Franceschi et al., 2018; Ghosh et al., 2022). This positions the microbiome gut–epigenome axis as a central therapeutic hub for broad-spectrum aging interventions.

Recognizing biotics and nutraceuticals as genuine Geroscience interventions has important clinical implications. Future longevity trials should evaluate these interventions using validated Geroscience endpoints such as epigenetic clocks, SASP profiling, microbiome aging indices, and multi-omic biomarkers, rather than limiting evaluation to conventional safety or metabolic endpoints. Moreover, combining biotics with pharmacological gerotherapeutics may offer complementary hallmark coverage and improve translational effectiveness in human aging interventions. The MELLOW Consortium's integrated framework, with its co-primary endpoints spanning gut metagenomic profiling, validated epigenetic aging clocks, leaky gut biomarkers, and systemic inflammaging indices, is designed precisely to operationalize this vision- providing the multi-site, multi-ethnic, multi hallmark clinical infrastructure through which the true Geroscience potential of biotics and nutraceuticals can, for the first time, be rigorously and comprehensively established.

## 7. CONCLUSION AND FUTURE PERSPECTIVES

The past decade has transformed aging science from a descriptive discipline into a mechanistically driven field capable of measuring, predicting, and increasingly modifying biological aging. The Geroscience hypothesis has shifted the focus from treating individual age-related diseases toward targeting the shared biological mechanisms that underlie aging itself. Advances in epigenetic clocks, senescence biomarkers, inflammaging indices, and multi-omic aging signatures have provided a robust framework for quantifying biological age and evaluating intervention efficacy in clinical settings.

These tools now allow aging to be studied as a modifiable biological process rather than an inevitable chronological outcome. The evidence synthesized in this review supports a compelling case for repositioning probiotics, prebiotics, postbiotics, and nutraceuticals as genuine Geroscience interventions rather than adjunctive wellness supplements. Unlike most pharmacological agents that target single pathways, biotics and nutraceuticals exert broader multi hallmark effects through the gut microbiome inflammaging–epigenome axis, mitochondrial function, cellular influencing senescence, immune regulation, intestinal barrier integrity, and systemic inflammation. Their accessibility, safety, and scalability further strengthen their translational value, particularly for diverse global populations where long-term pharmacological interventions may be less feasible.

However, realizing this potential requires a fundamental shift in clinical trial design. Future trials must incorporate validated biological aging markers-such as

 

epigenetic clocks, SASP profiles, gut microbiome aging indices, and intestinal permeability biomarkers-as endpoints, co-primary supported by harmonized and centralized analytical platforms to ensure reproducibility and comparability across studies. Integrative and combination-based intervention strategies, including biotics with pharmacological and lifestyle approaches, may offer the broadest hallmark coverage and the greatest potential for extending healthspan. Ultimately, the future of longevity medicine will depend not only on discovering new interventions, but on rigorously validating accessible and scalable strategies capable of modifying biological aging at population level. The MELLOW Consortium was founded on precisely this commitment. The work is underway.

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All authors have contributed to conceptualization, writing, reviewing, and critically revising the manuscript

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