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Intrinsic and environmental basis of aging: A narrative review

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ABSTRACT

Longevity has been a topic of interest since the beginnings of humanity, yet its aetiology and precise mechanisms remain to be elucidated. Aging is currently viewed as a physiological phenomenon characterized by the gradual degeneration of organic physiology and morphology due to the passage of time where both external and internal stimuli intervene. The influence of intrinsic factors, such as progressive telomere shortening, genome instability due to mutation buildup, the direct or indirect actions of age-related genes, and marked changes in epigenetic, metabolic, and mitochondrial patterns constitute a big part of its underlying endogenous mechanisms. On the other hand, several psychosocial and demographic factors, such as diet, physical activity, smoking, and drinking habits, may have an even more significant impact on shaping the aging process. Consequentially, implementing dietary and exercise patterns has been proposed as the most viable alternative strategy for attenuating the most typical degenerative aging changes, thus increasing the likelihood of prolonging lifespan and achieving successful aging.

1. Introduction

Rapid socio-economic and scientific developments during the second half of the 20th century have made fundamental changes in longevity and mortality rates across the global population, with an almost linear increase in life expectancy seen in some countries as the result of improvements in environmental and medical conditions [1]. This phenomenon is partly due to enhancements in early infectious disease management, nutrition, and control of cardiovascular risk factors such as hypertension and hypercholesterolemia [2,3]. However, it is concerning that other factors like obesity and diabetes combined with sedentarism have marked the beginnings of the 21st century and consequently led to a contrasting increase in the mortality rates associated with chronic degenerative diseases [4–6].

Interestingly, future life expectancy projections have stagnated in recent years instead of progressing in some countries leading to the hypothesis that rigorous control of cardiovascular risk factors, which initially decreased the mortality rates of cardiovascular diseases and strokes, has reached a plateau concerning its effects on longevity [7,8]. Another point of interest is that as life expectancy

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increases, so do the rates of age-related diseases, with prominent pathological entities such as cognitive decline, arthritis, cancer, and osteoporosis [9].

Since its beginnings, humanity has sought to extend its lifespan, favoring the emergence of a new branch of medical science focused on understanding the nature of aging to delay the process as far as possible. Aging is the root of multiple pathologies that increase the number of years lived with disabilities rather than mortality, i.e., as the elderly population increases and life expectancy rises, so do the chances of suffering from age-related diseases [10,11].

In light of the economic burden increase of fragile or chronically ill populations, it is crucial to deepen our understanding of the aging process and its implication on life quality to extend the individual's lifespan and healthspan [12,13]. Therefore, this review aims to comprehensively describe the currently recognized genetic, molecular, and environmental factors to understand better the aging mechanisms and the potential ways of implementing aging-delaying strategies.

2. Aging and longevity: in search of a consensus

Aging corresponds to the buildup of common morphological and physiological modifications that occur in all living organisms as time passes. However, it is heterogeneous and heterochronic since its pathology presents differently according to the individual's conditions and life stage [14,15]. Both genetic and environmental factors shape the aging process [16,17], causing cellular and molecular damage accumulation, which results in different types of cellular and tissue aberrations [18]. These conditions lead to multiple pathologies, such as cancer, cardiovascular and neurodegenerative diseases, or even individual death [19–25].

The origin of aging has been a matter of debate for decades [26], and several hypotheses proposing latent and complementary mechanisms for its evolution are under intense research. The dominant hypothesis explaining the ageing process are classified into two major groups: programmed theories and damage or error theories of aging [27] (Fig. 1). The programmed theories or adaptive theories of aging raise the notion that there is a deliberate deterioration with age since a short period of life results in evolutionary benefits [28]. This classification includes the mutation accumulation theory, which states that aging evolved through the accumulation of germline mutations that do not manifest until senectitude; therefore, ageing is the consequence of a diminishing force of natural selection that occurs with age. On the other hand, the antagonistic pleiotropy theory states that late-acting harmful genes are favoured by natural selection because of their benefits during early life stages [29]. Subsequently, a variation of the later-called disposable soma theory was proposed, which states the presence of energy-saving mutations beneficial to reproduction at the expense of reducing DNA repair capacity, ultimately increasing the speed of aging [30].

Similarly, the discovery of longevity genes paved the way for establishing the programmed longevity theory. This theory proposes the emergence of a longevity program during evolution that ensures the survival of the organism in extreme short-term stress conditions [31], allowing the expansion of lifespan when entering a maintenance period characterised by: increased stress resilience, diminished protein synthesis, and suspension of growth and reproduction, which brings as a benefit the reallocation of the organism's resources for the extension of lifespan in adults [32]. Finally, among the programmed theories is the Neuroendocrine Theory, based on the Hypothalamic-hypophyseal axis being responsible for aging via its mediation of energy homeostasis, hormonal regulation, and circadian rhythm through changes in neuronal regulators over time [33,34].

In contrast, the damage theories state that aging, rather than a programmed process, corresponds to the absence of selection for a maintenance mechanism. Consequently, it occurs because of the lack of natural selection in the post-reproductive stage [27,35]. Finally, within this classification, the one that stands out the most is the free radical theory, which states that aging is the collateral effect of not protecting tissues from the free radicals and oxidative stress that accumulate over time and cause DNA damage

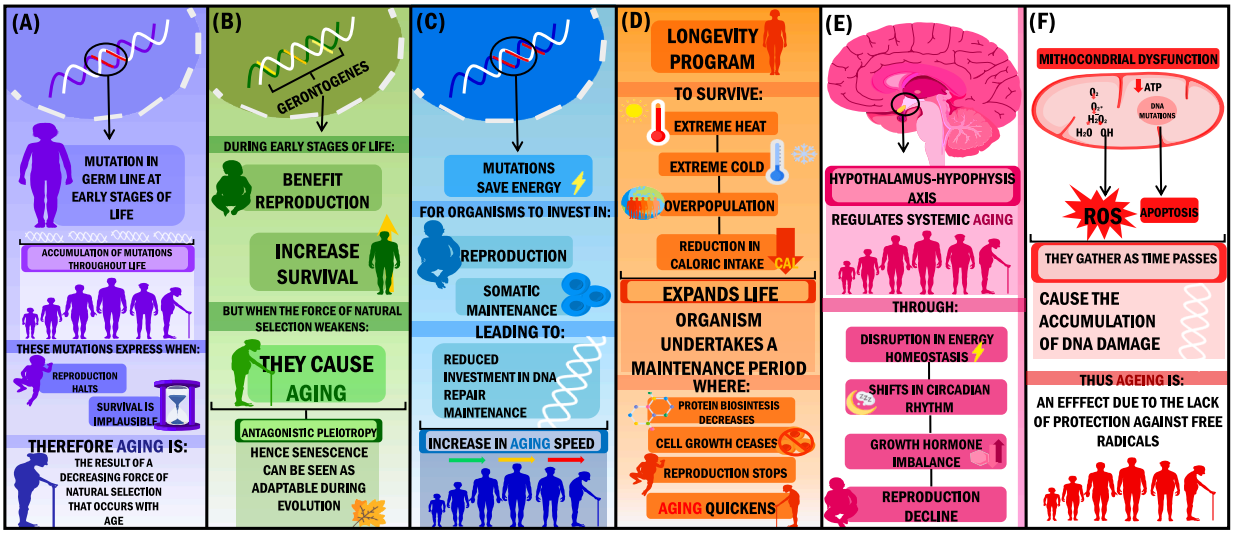

Fig. 1. Theories of aging.

accumulation; in addition, these react with different biomolecules, thus producing the pigmentation associated with aging [36,37]. Based on the review of the aging theories, it seems clear that aging is an adaptive phenomenon predominantly determined by genetics, the action of complex multicellular death programs along with the interaction and the relationship individuals have with their ecosystem.

Despite their different mechanisms, every theory of aging reaches the consensus that aging leads to functional decline and subsequent multiorgan tissue dysfunctions [35]. Even though understanding its biological origins is limited [38], scientists have identified common age-related characteristics known as hallmarks [39]. In this sense, the hallmarks are divided into three groups: primary, antagonistic, and integrative. Primary hallmarks are considered solely detrimental, one of which is genome instability or the accumulation of genetic damage over time. Usually, the cell's DNA repair mechanisms are enough to correct emerging mutations; however, its diminished actions in ageing and high rates of molecular damage ultimately lead to mutation buildup [40,41]. Another primary hallmark of aging is telomere shortening. Telomeres are non-coding nucleotide sequences found at chromosomal ends, whose function is to maintain genome stability. However, due to the nature of DNA replication machinery, telomeres lose some of their sequences after each round of cellular division, ultimately leading to cellular senescence [42,43].

Epigenetic alterations also enter into the primary hallmark category. These constitute a set of inherited gene expression changes that do not involve alteration of the DNA sequence, significantly determining cellular and tissue function during the aging process [44,45]. Furthermore, loss of proteostasis is another primary hallmark, distinguished by an accumulation or addition of misfolded proteins. Proteostasis is generally procured by a multi-compartmental system of regulators that ensures the correct folding of proteins; however, the function of this system deteriorates with age, which leads to reductions in cellular viability and alterations in protein turnover [46].

On the other hand, antagonistic hallmarks are beneficial in small amounts but become harmful in excessive levels. Dysregulations of nutrient sensors characterise this category. In this way, the homeostatic mechanisms that maintain physiological blood glucose levels are altered, affecting the metabolic integrity of the organism [40]. Another instance of an antagonistic hallmark is cellular senescence, which corresponds to the state of cell cycle arrest and phenotypic variations. As senescent cells accumulate, the release of pro-inflammatory factors, metalloproteinases, and age-related growth factors increases, thereby marking its association with the aging process [47]. Finally, mitochondrial dysfunction also enters into this classification, resulting from a decline in mitochondrial integrity with age. The main consequence of this hallmark is the diminished efficacy of the ATP-producing machinery in the respiratory chain, thus increasing the number of free radicals responsible for biomolecular damage [48,49].

Lastly, integrative hallmarks affect cellular homeostasis through stem cell depletion and cellular communication impairment. Stem cell depletion, defined as the significant reduction or increase in tissue regenerative capacity, correlates with the accumulation of DNA damage, overexpression of cell cycle inhibitory proteins, and telomere shortening. Meanwhile, impaired cellular communication constitutes all the age-related endocrine and neuronal changes that result in the dysregulation of neurohormonal signalling and increase of inflammatory reactions with the underlying decrease in immune response leading to aging [38] (Fig. 2).

The set of discoveries from the origin of aging to its distinguishing hallmarks represented the cornerstone for the introduction of new concepts that continue to revolutionize our perception of aging [38]. A clear example is the characterization of phenotypes that are related to this process, determining four distinct patterns and/or types of aging known as *ageotypes* described for the first time in the longitudinal multiomics trial conducted by Ahadi et al. the results showed that individuals age to different degrees through different

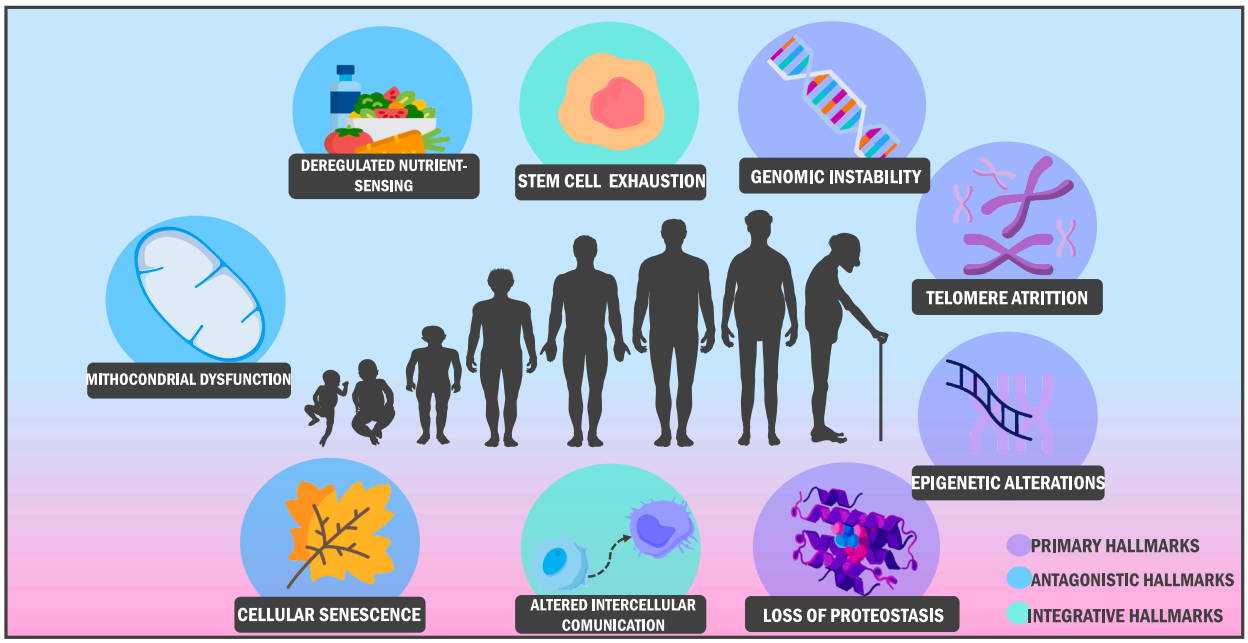

Fig. 2. The hallmarks of aging.

molecular and cellular mechanisms, while at the same time, they were able to elucidate the signaling pathways that are most active during aging: immune, metabolic, kidney and hepatic pathways; evidencing individuals who presented a more pronounced aging-related activity in the kidney signaling pathways and others who presented the four active pathways [50,51].

However, it was also observed that the signaling pathway which is most related to aging is the cardiac pathway, suggesting the existence of more signaling pathways related to aging, therefore, it is valid to profile a larger number of individuals to determine which other pathways are perhaps more closely related to this phenomenon. Undoubtedly the discovery of these patterns and types of aging unfold new alternatives for the creation of diagnostic strategies and treatments that could potentially slow aging and prolong longevity [50,51].

3. Intrinsic aging bases

Why aging occurs and how it links to its many co-morbidities has been a subject of intense debate for decades. Several intrinsic and extrinsic factors constantly interact synergistically to mediate the aging process; therefore, both need to be thoroughly described to obtain a clear view of the underlying processes of this phenomenon. This understanding is particularly relevant when considering how one individual's aging process cannot be wholly equated to another's, seeing as the interplay between intrinsic and extrinsic factors will never be the exact same in two different individuals, even when they are part of one community, thus rendering any attempt at "standardizing" aging as rudimentary at best and an exercise on futility at worst [52].

Regarding the intrinsic basis of aging, the impact and interaction between select candidate genes related to longevity and their variations, as well as epigenetic factors and other primary hallmarks of cellular aging have been suggested as the main culprits of the aging process, in conjunction with specific molecules and cellular organelles such as metabolites and mitochondria, respectively [53,54].

3.1. Telomere shortening

Telomeres are repetitive nucleotide sequences at the ends of chromosomes that prevent chromosomal instability and end-to-end fusion. Unfortunately, telomeres are shortened on each cellular division cycle limiting the number of possible divisions a cell can engage in, which suggests the existence of a mitotic clock involved in aging [55]. The resulting instability is the prelude to a series of metabolic and cellular events that lead to apoptosis, cellular senescence, genome instability, and concomitant changes in cellular morphology and secretory patterns [56–58]. However, recent studies have cast doubt on the determining nature of this clock in aging since telomere shortening could be a direct indicator of ROS-mediated cellular stress. Furthermore, guanine residues are abundant in telomeres, which are particularly sensitive to ROS exposure; therefore, this kind of cellular assault can affect telomere integrity and subsequently lead to telomere dysfunction [59–61].

3.2. Genome instability

Genome instability refers to the structural DNA changes provoked by mutations and accumulated damage. Intrinsic (e.g., errors in DNA replication and oxidative stress) and extrinsic (e.g., radiation) factors play prominent roles in genome instability development. These molecular assaults occur thousands of times daily; however, DNA repair mechanisms have evolved to deal with these daily lesions, allowing the maintenance of genome stability [62,63].

Multiple studies have implicated genome instability in the aging process. Considering the role of DNA repair mechanisms in genome stability, its importance concerning aging has been intensively debated. DNA repair pathways are affected by aging, losing efficiency, and failing to prevent damage buildup. This reduction in repairing capacity results from a decreased expression of relevant proteins [64,65]. There is some controversy regarding the importance of these mechanisms in human longevity since while certain studies indicate the presence of related gene polymorphisms in long-lived individuals and a higher DNA repairing capacity in centenarians, other studies point out that the DNA repairing capacity of centenarians is similar to that of younger cohorts, which opens the field for further study in the subject and inescapably underlines the variability provided by other extrinsic and intrinsic factors that might at some level modify the elements involved in DNA repair mechanisms in any given individual [66,67].

3.3. Genes and signaling pathways associated with longevity

The highly conserved insulin and insulin-like growth factor 1 (IGF-1) signaling pathways and their relation to longevity in invertebrate and vertebrate species have paved the way for research on its involvement in human longevity [68]. Even though the exact processes by which this signaling cascade influences aging have not been completely elucidated yet, epidemiological studies have determined a clear relationship between the two [69].

Several studies have focused on assessing the effects of changes in the functioning of insulin-like growth factor 1 (IGF-1) and its receptor (IGF-1R) on aging murine models. However, results have proven controversial, with a marked unexplainable sexual dimorphism that favors females. In addition, mutations with complete functional loss of IGF-1R result in high mortality of murine models during their first days of life, while mutations with partial function loss lead to an extension of lifespan in females [70,71].

Concerning human populations, single nucleotide polymorphisms (SNP), originating from point mutations in the IGF-1R and FOXO3 alleles, have been observed in epidemiological studies of centenarians, with heterozygous mutations of IGF-1R resulting in attenuated insulin/IGF-1 signaling pathway (IIS) and high serum IGF-1 levels in females. Similarly, low serum IGF-1 levels have been

found in elderly subjects, emerging as a predictor of human longevity [72,73]. More studies are needed in both human and murine populations to, if not entirely describe the mechanism linking IGF-1R to human longevity, at the very least to accurately pinpoint its involvement and effect in the aging process and what the hinted-at sexual dimorphism in murine populations would entail in human populations, leading to the question of how aging is approached in both men and women and whether these approaches should differ at all [74].

The intimate relationship between the FOXO family, especially FOXO3, and IIS suggests a complex network of metabolic pathways that interact to achieve a longevity phenotype. Multiple pathways where transcription factor FOXO3 could influence the aging process have been described, involving energy metabolism, cell cycle regulation, apoptosis, and oxidative stress [75]. FOXO3 has been consistently linked to aging in both animal models and human studies, with the presence of multiple SNPs prevailing in human subjects [76]. Although how FOXO3 and its various SNPs influence aging has not been elucidated in virtue of the significant number of genes that it regulates, it is essential to emphasize that the presence of FOXO3 SNPs in multiple elderly populations throughout the world and its IIS inhibitory capacity define it as a critical subject for future research [77,78].

As previously mentioned, genetic factors independently are insufficient to comprehend the aging process in the entirety of the global population, which is supported by the reduced replicability of a so-called "long-lived genotype". This can stem from both the environmental and extrinsic variations that accumulate and impact the expression and effects of these genes, as well as a reduced sample size available for study [79]. Additionally, it is notable that, contrary to IGF-1R, there seems to be a stronger association between FOXO3 variants and extreme longevity in males as opposed to females, further highlighting the need to study this phenomenon from the perspective of sex-mediated differences in aging [80].

The role of APOE in aging has been focused on neurodegenerative diseases typical of old age, especially Alzheimer's Disease (AD), considering its role in the transport of lipids to the central nervous system and its support of neuronal maintenance and repair. Polymorphisms in the APOE alleles have been consistently associated with human longevity, making APOE4 and APOE2 the most studied members [81,82]. These proteins show opposing relations regarding the aging process, with APOE4 being considered a risk factor for the development and progression of AD, while APOE2 is described as a protective factor instead. APOE4 has also been related to adverse effects on brain vasculature and dysfunction of the blood-brain barrier, suggesting a second mechanism implicated in the neurodegenerative process, particularly the one seen in AD [83,84].

On the other hand, APOE2 has been pointed out as a protector of longevity in different epidemiological studies, occurring most frequently in the elderly and centenarians of different populations that age healthily, while APOE4 has marked a higher probability of early mortality in older adults. Furthermore, some studies have sought to elucidate the role of APOE2 in aging independently of its role in AD, finding in murine models without AD that APOE2 positively influences longevity, preserving levels of activity, locomotion, and exploration that tend to decrease with age [85,86].

3.4. Epigenetic factors

Initially, hypotheses destined to explain the bases of aging were mainly oriented toward changes in the genetic makeup; however, in recent years, distinct epigenetic modifications have been gaining recognition to become a hallmark of aging. In fact, epigenetic markers are considered the most reliable estimate of biological age and, health status [87,88]. For instance, the "epigenetic drift", a group of age-related changes in epigenetic patterns, appears to be caused by stochastic and programmed biological factors [89,90]. Among the most notable epigenetic alterations are variations in DNA methylation patterns [91,92]. Numerous studies have associated aging with global genome hypomethylation states, especially in promoter regions, exons, introns, intergenic sequences, and repetitive elements (Alu/L1). Consequently, loss of general methylation may constitute a triggering factor for genome instability associated with aging and neoplastic states [93–98].

Moreover, hypotheses have been formulated that postulate hypomethylation as a consequence of the diminished enzymatic action of DNA Methyltransferases (DNMT1 and DNMT3a), both of which are methyltransferases that catalyze the addition of a methyl group to nitrogenous bases. On the other hand, alternative hypotheses suggest that hypomethylation is partially caused by random errors in the replication of methylation patterns from the template strand to the daughter strand or during the maintenance of methylation; however, these hypotheses fail to explain why such losses are site-specific [99,100]. Simultaneously, certain specific genomic areas are hypomethylated overtime to silence the expression of genes involved in transcription, tumor suppression, development, growth, and metabolism, suggesting that these changes could lead to enzymatic aberrations of DNMT and other related enzymes that, in turn, would generate anomalies in gene expression [101].

Histone modification is another age-related epigenetic alteration, and eight modification types are known to date, among which methylation and acetylation are prominent [102,103]. Furthermore, several clinical trials have demonstrated the influence of histone tail modifications on gene expression, resulting in suppression or abnormal activation of genetic loci and consequently leading to genome instability [104–108]. In addition to these processes, histones can suffer other kinds of modifications, from the exchange of histone proteins with functional and structural variants to the reduction in the number of histones that occur during aging, generating reductions in the volume and setting of nucleosomes and thus affecting global chromatin structure [109–112].

Changes in chromatin structure are, in turn, a distinctive modification of senescent cells [113,114]. Recent research has pointed to chromatin loss as a regular process in aging cells, capable of producing changes in nuclear architecture and consequently altering gene expression in that region [115,116]. It is currently proposed that chromatin loss may induce senescence due to a process known as chromatin redistribution, whereby euchromatin regions become heterochromatized [117]. Such configurational variations in histone, enzyme, and chromatin components exert a negative influence on genetic homeostasis by promoting transcriptional deregulation and genome instability, resulting in diverse abnormal phenomena such as double-strand breaks, formation of damaged loci, translocations,

insertion of mitochondrial DNA (mtDNA) into the nuclear genome, and retrotransposition [45,118].

The role of small ribonucleic acid molecules called non-coding RNAs (ncRNA) has been recently recognized in the epigenetic context, owing to its capacity to manipulate gene expression without affecting gene sequence. In this way, ncRNAs intervene in numerous cellular processes, including aging and senescence [119,120]. Although its molecular mechanisms have not been elucidated, specific ncRNAs, such as long non-coding ARNs (lncRNA), may influence chromatin structure through interactions with chromatin-modifying enzymes and thereby induce age-related gene suppression. Additionally, reductions in the activity of microRNA have been linked to advanced age, with some members of this family possessing anti-aging properties, while others act in favor of aging in nematodes such as *Caenorhabditis elegans* [121,122].

In summary, while there has been recent and vested interest in identifying and describing the epigenetic mechanisms involved in the aging process following the recognition of their importance and value in their interactions with other extrinsic and intrinsic factors, there is still much to be explained regarding their specific functioning and its implications concerning human longevity and aging.

3.5. Mitochondrial role

Following advances in mitochondrial function and metabolomics in the last decade, a correlation between several metabolites levels with aging has been observed (Fig. 3). In this sense, metabolites capable of controlling aging may act as novel biomarkers, helpful in elucidating its underlying mechanisms [123,124]. According to the theory of aging by free radicals, aging is the consequence of oxidative damage inflicted by reactive oxygen species (ROS), including superoxide, hydroxyl, peroxyl radicals, and hydrogen peroxide, among others. For example, a study conducted by Iatsenko et al. on a Drosophila fly model observed shortened lifespans after an NADPH oxidase-dependent increase in ROS [125]. Likewise, another study, which compared antioxidant defences in blood samples from 184 older adults (age 65 to 90) with that of 37 younger adults (age 55 to 59), found a statistically significant decrease in the activity of Zn, Cu-, superoxide dismutase (SOD-1), catalase (CAT), and glutathione peroxidase in the older cohort [126]. Even though it is not clear how ROS induce aging, the modifications these molecules produce on carbohydrates, lipids, proteins, and DNA through oxidation are the most likely culprits. These molecular assaults lead to lipid peroxidation and glycoxidation, which ultimately set off a chain reaction that ends in various cell function alterations [127]. In this sense, it would seem logical to paralelly correlate the aging process along with certain chronic diseases associated with increased ROS levels, such as, arterial hypertension, insulinresistance, atherosclerosis or neurodegenerative diseases [128,129].

Autophagy involves the lysosomal self-degradation of cell material for cellular homeostasis, another age-related process strongly linked to specific metabolites [130]. It is currently known that autophagy decreases with age, promoting the accumulation of misfolded proteins and cellular dysfunction [131]. In addition, autophagy depends on energy availability, a prominent downregulation signal for the mammalian target of rapamycin (mTOR). This pathway promotes anabolism while suppressing protein catabolic processes such as autophagy [132]. In a study conducted on an induced aging brain rat model, Wang et al. found that mTOR downregulation counteracted the dysfunctional autophagy seen in the model, which led to the recovery of its anti-aging effects and increased learning and memory capacities [133].

Finally, another theory to be considered is the glycation theory, which suggests that glucose acts as an aging mediator by inducing the accumulation of advanced glycation end-products (AGEs) [134]. Glycation is a spontaneous non-enzymatic mechanism that

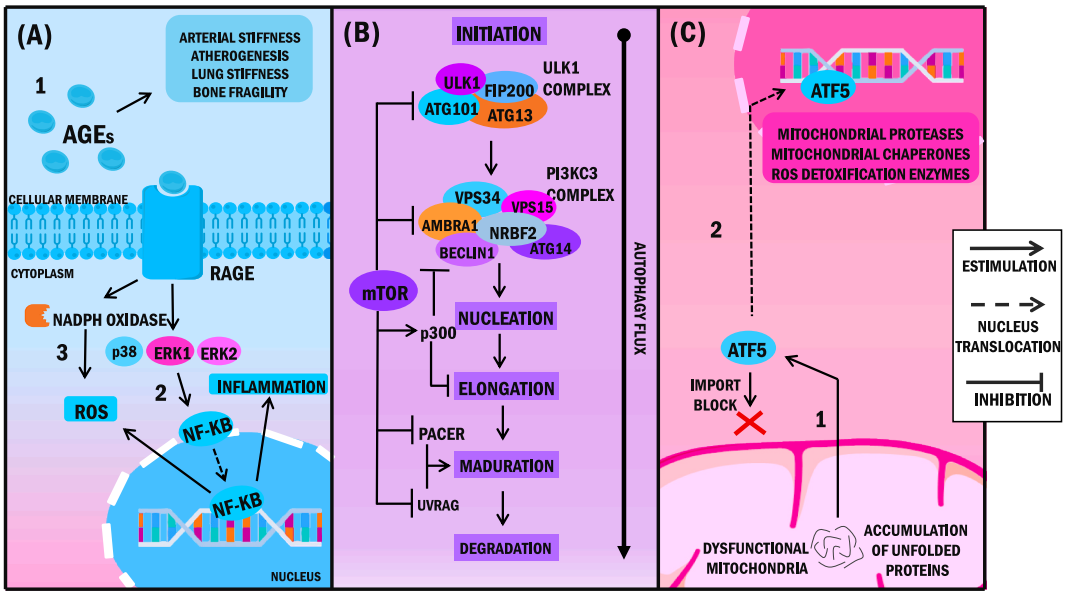

Fig. 3. Metabolomic and mitochondrial pathways related to aging and longevity.

increases during diabetes, inflammation, and renal insufficiency [135]. It starts with a hyperglycemic state or oxidative stress that induces a chemical reaction between free amine residues and sugars/aldehydes molecules, forming a Schiff base that posteriorly rearranges into an Amadori product. These intermediary products suffer irreversible oxidation, polymerisation, dehydration, and reticulation reactions, resulting in the formation of AGEs. These modified macromolecules accumulate significantly in different tissues and organs, causing functional loss [136]. AGEs are believed to contribute to aging and the onset of age-related diseases by three mechanisms: accumulation of AGE in the extracellular matrix (ECM), which reduces connective tissue elasticity [137]; glycosylation of intracellular proteins, leading to loss of cellular function [125]; and finally, activation of inflammatory signaling, ROS overproduction, mitochondrial dysfunction, and subsequent apoptosis, all of which are products of the interaction between AGEs and their cellular receptor RAGE [138].

Moreover, mitochondria are cellular organelles that act as integrating centres of metabolism, as well as producers of adenosine triphosphate (ATP) and regulators of redox homeostasis. There is an inverse correlation between mitochondrial function and aging and, therefore, to age-related diseases, particularly neurodegenerative diseases. For this reason, mitochondrial dysfunction and the accumulation of damaged mitochondria are considered hallmarks of aging (Fig. 3).

Oxidative phosphorylation (OXPHOS) is the most efficient energy-producing pathway and the leading producer of ROS at the cellular level. Mitochondrial oxidative stress may result in mtDNA mutations because of its particular vulnerability due to its proximity to ROS production sites [139]; this is why mtDNA has a significantly higher mutation rate and a lower repairing capacity than nuclear DNA (nDNA). This phenomenon leads to the production of dysfunctional electron transport chain complexes, further incrementing the production of ROS and, in turn, the oxidative damage to macromolecules and mtDNA [140].

Mitochondrial damage can be mitigated by fusion and fission events associated with mitochondrial dynamics, modulating mitochondrial quality and protecting them from mitochondrial stress [141]. Mutations in fusion and fission-related proteins, such as mitofusin 1/2 (MFN1/2), optic atrophy 1 (OPA1) gene and dynamin-related protein 1 (DPR1), mitochondrial fission factor (MFF), mitochondrial fission protein-1 (FIS1), mitochondrial dynamics protein D49 (MID49), and mitochondrial dynamics protein D51/mitochondrial elongation factor 1 (MID51/MIEF1), are known to lead to reduced lifespan in the face of the accumulation of dysfunctional mitochondria throughout age [142,143].

On the one hand, mitochondrial fusion overexpression increases bioenergetics and ATP production efficiency, while fragmentation by fission is associated with lower ATP production and more significant oxidative stress [144]. On the other hand, in another study, a greater mitochondrial volume in conjunction with OPA1 and MFN1 overexpression was observed in aged cells [145]. In turn, a study by Rana et al. using *a Drosophila melanogaster* model with transgenic expression of DRP1 in middle age showed prolongation in useful life while improving mitochondrial morphology.

The accumulation of protein damage and mitochondrial proteotoxic stress increase with age due to rising ROS levels in mitochondrial dysfunction. The mitochondrial unfolded protein response (UPRmt) is the pathway that ensures mitochondrial proteostasis by increasing the expression of mitochondrial chaperones and proteases [146]. For this reason, the UPRmt has been suggested to be intimately related to longevity. A study that modulated levels of ATFS-1 (a mediator of UPRmt) in *Caenorhabditis elegans* observed a

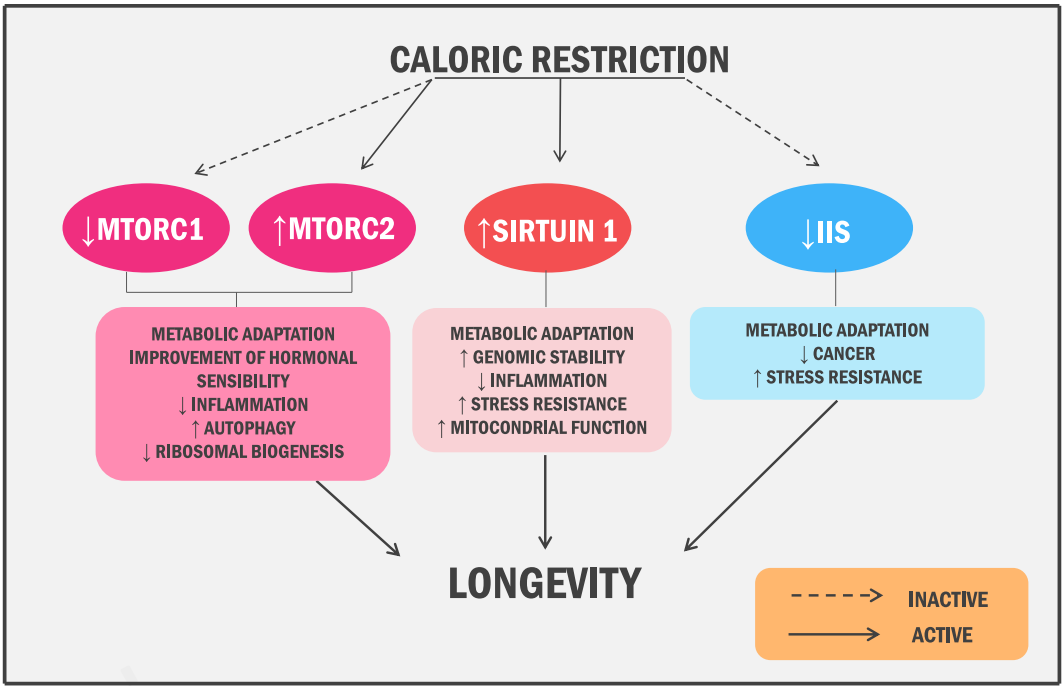

Fig. 4. Nutrient sensing pathways influencing longevity.

lengthening of lifespan [147], which is of particular interest because a human counterpart of ATFS-1, called ATF5, was recently identified [148,149]. Nonetheless, the vast majority of mitochondrial dysfunction studies have been performed non-human models, thus, more clinical trials regarding mitochondrial pathologies and aging are necessary.

4. Extrinsic or environmental aging bases

Various environmental factors related to current lifestyles, such as hypercaloric diets, sedentarism, and harmful habits, can accelerate the aging process due to their detrimental metabolic consequences [150]. In this regard, physical fitness has been linked to longevity [151]. Recent studies suggest that physical activity (PA) preserves telomere length. In this respect, less active individuals seem to have shorter telomeres compared to those who exercise regularly, with a 200 nucleotide difference corresponding to 10 years of life [152,153]. Another study suggests that moderate PA could be more beneficial than low or high PA since it shows a higher positive effect on telomere length in individuals who practice it in middle age [154]. Another exciting fact is that PA seems to positively affect the expression of skeletal muscle markers involved in longevity pathways. Long-term aerobic exercise has proven to increase SIRT1 and SIRT3 expression in older rats, while high resistance training bolstered the expression of heat shock proteins in rat skeletal muscle [155] (Fig. 4).

Mancini et al. [156] suggest that lifelong training increases the expression of messengers involved in self-lysosomal and proteasome-mediated degradation machinery (RAD23A, HSPB6, RAB1B, TRAP1, SIRT2, and HSBPB1), cell growth and differentiation processes (RPL1, RPL4, RPL36, and MRLP37), and promotion of autophagy and proteasome processes (protein complex Bcl-2, HSP70, HSP90, PSMD13, and ATG5-ATG12) in skeletal muscle samples compared to untrained controls of the same age. Since autophagy is a catabolic process that is deteriorated with age, its PA-mediated activation could physiologically facilitate the turnover of most cellular organelles and membranes of aged cells, preserving cellular function [157–165].

On the other hand, harmful habits, such as smoking, can accelerate the epigenetic age and reduce life expectancy via DNA hypo- or hypermethylation in CpG sites [166]. Although a reversal in methylation is observed upon cessation of smoking, its magnitude depends on the initial intensity of the habit [167]. At the same time, smoking has been associated with multi-pathway dysfunction, including the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway, lipopolysaccharide response pathway, and Tumor Necrosis Factor signaling pathway [168]. Furthermore, smoking is also thought to influence telomere shortening and, thereby, genome stability [169].

Table 1
Influence of dietary patterns in longevity and age-related diseases.

	Sample Size/Subjects	Duration	Results	References
Portfolio/ Mediterranean Diet	72 individuals	48 ± 12 days	Assesments of individuals on portfolio and portfolio/mediterranean diet resulted in a short term 25% reduction of LDL levels in patients with hypercholesterolemia.	Ferro et al. [203]
DASH diet	12 cohort studies (548.632 individuals)	5.7–24 years	Higher adherence to DASH diet was linked to reduced risk of stroke. RR 0.88, 95% and CI 0.83–0.93.	Feng et al. [204]
Calorie-Restricted DASH diet	36 individuals	12 weeks	Body weight decreased by 6.3%, body fat decreased by 2.5%, AFM decreased by 4.4 kg, while REE, handwgrip strenght, gait and balance were maintained.	Perry et al. [205]
Caloric Restriction	29 articles (704 subjects)	–	Reduction of body weight, BMI, fat mass, total cholesterol, glucose, insulin levels.	Caristia et al. [206]
Mediterranean Diet	3128 older adults	1 year	Lower NAI score was associated with mediterranean diet and successful aging (−0.03, 95% CI -0.5 to −0.006)	Tyrovolas et al. [207]
Mediterranean Diet	1010 older adults	2 phases: 1 year and 6 years	Reductions in weight gain, blood pressure, total and HDL cholesterol.	Castellana et al. [208]
Caloric Restriction	C57BL/6 mice	3 months	Attenuation of age-associated adipocyte enlargement and prevention of the age-related decline in beiging potential of WAT.	Sheng et al. [209]
Caloric Restriction	Drosophila Melanogaster	CSS	CR extended lifespan and reduced reproduction irrespective of injury and infection.	Savola et al. [210]
Okinawan Diet	16,498 individuals	3 years	No statistically significant association between total Okinawan vegetable consumption and risk of stroke and coronary heart disease was obtained 1.09 (95% confidence interval, 0.93–1.29; P for trend = 0.289)	Yoshizaki et al. [211]
Okinawan-Nordic Diet	–	28 weeks	Reduction in body weight (7%) ($p < 0.001$), body mass index ($p < 0.001$), and waist circumference (7.0 cm) ($p < 0.001$), levels of C-peptide ($p = 0.015$), triglycerides ($p = 0.009$), total cholesterol ($p = 0.001$), and low-density lipoprotein-cholesterol ($p = 0.041$), systolic blood pressure (9.6 mmHg) ($p < 0.001$), diastolic blood pressure (2.7 mmHg) ($p < 0.001$), and heart and respiratory rates ($p < 0.001$) and cortisol ($p = 0.015$).	Darwiche et al. [212]
Mediterranean Diet	4896 individuals	13 years	High rMED is associated with mean age at death [POM 90.16 (95% CI 86.06, 94.25)]. Subjects with low and medium rMED showed lower lifespan, 5.62% (95% CI 1.01, 10.3) and 9.90% (95% CI 5.30, 5.30), respectively.	Campanella et al. [213]
Caloric Restriction	218 individuals	2 years	Moderate CR, 11.9% on average, induced improvements in aging-related biomarkers	Dorling et al. [210]

Regarding drinking habits, studies indicate it is more probable to achieve longevity when consuming 5–15 g of alcohol per day (0.5 to 1.5 glasses per day) [170]. Accordingly, other studies suggest that moderate alcohol consumption could play a role in healthy cognitive longevity while reducing the risk of chronic diseases such as cardiovascular disease [171]. In this respect, wine is the preferred option since it contains various substances, e.g., flavonoids, beneficial to health. Resveratrol, in particular, has shown a positive effect on SIRT1 expression, in addition to its antioxidant, anti-inflammatory, and anti-tumor properties and the upregulation of the anti-apoptotic and redox proteins Akt and Blc-2 [172]. On the other hand, multiple studies point out that excessive consumption is associated with higher disease risks, higher epigenetic aging rates in healthy individuals, and premature death [173,174]. Therefore, the role of alcohol in aging depends on multiple factors, including the amount and frequency of its consumption [175].

On a different line, air pollution has become a major public health concern. Air pollutants are considered a mixture of chemicals and particles in the air such as nitrogen oxides, sulphur oxides, tropospheric ozone, volatile organic compounds. These compounds enter the respiratory tract leading to severe *in situ* damage in addition to affecting the body as a whole through different mechanisms [176]. It has been proven that acute exposure would result in high levels of reactive oxygen species (ROS), together with mitochondrial dysfunction and the consequent energy deprivation. Whereas prolonged stimulation, even if mild, would result in a constant production of ROS and chronic low-grade inflammation, potentially increasing disease risk and promoting pathological aging [177]. In addition, Martens et al. [178] suggest that air pollutants can produce DNA mutations that encourage carcinogenesis and impair telomerase activity, causing ongoing DNA damage and premature aging.

The relationship between aging and psychological factors has been the subject of multiple studies. Stress may have pathophysiological effects that contributes to immune response dysregulation and possess long-term impacts on aging [179]. The presence of acute short-term emotional stress increases circulating inflammatory indicators via catecholaminergic activity. Furthermore, chronic stress promotes the development of several age-related pathologies by constantly activating the hypothalamus-pituitary-adrenal axis, resulting in chronic elevations of systemic glucocorticoids, affecting the balance of the T helper cell type 1/type 2 cytokine networks, this phenomenon exacerbates the defective immune response observed in aging [180]. Additionally, there is an impairment of the antioxidant defense system to manage ROS production after chronic stress, resulting in the damage of tissues; it has been demonstrated as well that people exposed to chronic stress show a faster telomere shortening in their cells [181]. In this regard, it is crucial to emphasize the promotion of healthy lifestyles and social support networks [182]. Finally, socio-economic status and life conditions continue to be essential moderators, hence, those with lower incomes generally tend to have a less healthy diet, eating foods rich in saturated fats and sugars and low in antioxidants and essential fatty acids, since a healthy diet usually has a higher cost [183,184].

4.1. Healthy aging and longevity: a question of lifestyle?

Based on the above, the tremendous impact of psychobiological habits on human lifespan extension is irrefutable [185–196]. Furthermore, various studies suggest that environmental factors may have a more decisive influence than genetic phenomena [197–200] (Table 1). Nutrition plays a vital role in lifespan extension and successful aging; therefore, potential dietary strategies to increase longevity have gained much scientific interest [201,202].

In this regard, CR represents the most reproducible method to extend life expectancy. CR reduces caloric intake below energy requirements without interfering with metabolic homeostasis and optimising nutrition [206,214–217]. Studies indicate that long-term CR could increase human life expectancy by three to five years. Furthermore, despite the lack of evidence regarding its underlying mechanisms in humans, numerous pre-clinical studies report the influence of CR on different age-related phenomena [210]. CR is believed to induce a cellular transition from proliferative to energy maintenance, avoiding substrate wasting and prolonging long-term cell survival. In addition to increasing resistance against genetic damage, improving antioxidant defences, mitochondrial biogenesis, autophagy, cell metabolism, oxidative stress, genomic maintenance, protein synthesis, and the prevention of inflammation mediated by modifications in gut microbiota and the activation of pathways such as SIRT1, mTOR, 5′ AMP-activated protein kinase (AMPk), IGF-1, peroxisome proliferator-activated receptor (PPARP), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PCG-1α), and growth hormone (GH) [218,219]. CR-modulating effect on these metabolic pathways results in weight loss, reduced chronic disease severity, and the action of intrinsic aging mechanisms [220,221]. Despite these benefits, CR is considered an unfeasible intervention in humans due to its low long-term adherence. For this reason, alternative interventions that have comparable benefits through similar or independent mechanisms have been proposed, such as intermittent fasting, certain foods such as nutraceuticals, or reduced amino acid intake [222–225].

While reducing caloric intake is emerging as the most effective technique to increase longevity, particular interest must be given to the quality of the ingested nutrients [226]. Throughout the years, different nutritional regimens have been designed, generally based on a high intake of vegetables, fruits, legumes, and complex carbohydrates, with moderate monosaturated fats, lean meat, and fish [227]. Consequently, their high contents of phytonutrients and bioactive compounds provide antioxidant, anti-inflammatory, and thermogenic properties, thereby decreasing glycemic load, inflammatory states, and oxidative stress levels and promoting a potential modulation of age-related pathways [228,229].

In this context, the Okinawa Islands inhabitants in Japan hold the title of the population with the most extended lifespan, with five times the more significant proportion of centenarians and a reduced prevalence of age-related diseases [209]. Research to determine the causes of longevity in these individuals concludes that the Okinawan lifestyle and nutritional habits are the main reason [201,230,231]. Furthermore, the concept of the Okinawan diet was suggested, based on the traditional meals of that region, as a potential strategy to increase life expectancy and reduce age-related co-morbidities [207]. Although The Okinawan diet is low in calories and fat, its high amounts of phytonutrients and polyphenols, as well as its high carbohydrate-to-protein ratio (10:1), make it a nutritionally rich regimen [232]. Given its low caloric intake, the Okinawan population has been considered a model of caloric restriction. The most

commonly consumed foods are miso soup, sweet potatoes (as the primary source of carbohydrates), abundant vegetables and legumes, bitter melon (*gyu*), algae, tofu, herbs, spices, soy, green tea, kohencha tea, and low proportions of red meat, dairy, noodles, fish, and alcohol [207,233,234].

Nevertheless, the Okinawan population is not the only one presenting low morbimortality rates and healthy aging [235]. The inhabitants of the Mediterranean are recognized for their balanced diet and frequent physical activity [205]. Despite regional variations, Mediterranean dieting habits are considered the healthiest dietary patterns in the world [236]. Based on this principle, the Mediterranean diet gained public and scientific interest, being characterized by the consumption of abundant vegetables, fruits, cereals, grains, nuts, seeds, olive oil as the primary source of fat, cheese, yoghurt, moderate consumption of red wine and proteins such as fish or chicken, as well as limited intake of red meat and eggs [204]. Thanks to its components, the Mediterranean diet is high in antioxidants, omega-3, omega-6, polyunsaturated fatty acids, polyphenols, fibre, folates, carotenes, vitamins, and minerals. In turn, these molecules have antioxidant and anti-inflammatory properties that decrease oxidative and genetic damage, modulate age-related pathways, stabilize telomere length, maintain proteasome function, and increase autophagic phenomena [203,211,212,237–241]. In this way, the Mediterranean diet could generate increases in life expectancy, cognitive function, prevention of neurodegenerative diseases, and reduction of the risk of developing some types of cancer in the long term [208,242].

On the other hand, nutritional strategies originally aimed at co-morbidities prevention, such as the DASH (Dietary Approaches to Stop hypertension) and portfolio diets, also include lifespan extension among their lists of benefits [232]. In this respect, the DASH diet is one of the most used dietary patterns for high blood pressure prevention. This diet includes abundant vegetables, fruits, grains, birds, fish, low-fat nuts, seeds, and dairy products, along with a limited intake of sodium, sugar, lipids, and red meats. Similarly, the Portfolio diet, designed to reduce serum cholesterol levels, is mainly based on vegetables, beans, oatmeal, soy, margarine, and almonds [243].

Likewise, physical activity has reported multiple anti-aging effects, e.g., prevention of severe muscle atrophy, maintenance of cardiorespiratory conditions and cognitive function, and increased metabolic activity. This approach reduces the risks of different co-morbidities, mitigates physiological changes, and augments life quality [171,244,213]. Numerous studies have targeted identifying the role of physical activity in various age-related phenomena, concluding that aerobic exercise and resistance training produce changes in each of the hallmarks of aging [245]. Furthermore, long-term aerobic exercise may optimise DNA-repairing mechanisms, thus preventing genome instability [246].

Moreover, physical activity may promote changes in the regulation of several kinds of proteins involved in DNA protection, repair, and cell cycle regulation, which could positively impact telomere length and induce the expression of telomerase-stabilising proteins. Furthermore, physical activity is also thought to counteract mitochondrial dysfunction and reduce the risk of cancer since it promotes mitochondrial biogenesis and increases natural killer (NK) cell activity and the secretion of anti-tumor myokines [247]. Finally, exercise benefits could extend to stem cell replenishment and intercellular communication since reducing mitochondrial ROS levels and improving the endogenous antioxidant profile fosters pluripotent stem cell activation and restores defective cell signaling pathways [248]. To obtain these benefits, The American College of Sports Medicine recommends the performance of aerobic, strength, resistance, flexibility, and neuromotor exercises, ideally with professional supervision. In this respect, the intensity and difficulty level of the exercise regimen must be modified according to factors such as the individual's fragility, tolerance, personal preference, and necessities. Lastly, it is recommended to continue the exercise program even after the disappearance of co-morbidities to maintain the therapeutic benefits [249].

Finally, although most of these techniques have been practiced for years or even centuries, there is still a lot more to be discovered and improved in regards to longevity, since all of these nutrition patterns and other habits have not been designed to enhance longevity but instead, have emerged from merely cultural traditions or as a way to improve certain chronic diseases, many questions arise, is there a way to combine each technique or create new approaches to obtain the ideal nutrition pattern to increase longevity?, are there any other undiscovered nutrients, supplements or conducts to enhance life expectancy?, can science transcend the modification of psychobiological habits and create novel procedures through recent advances in genetics, epigenetics, metabolomics, among other scientific fields in constant expansion?, and thus transform the concept of longevity from unpredictable and unknown to a more precise and manageable outcome. In present, all these interrogants remain unanswered, more clinical trials of different longevity approaches with more subjects and following periods are necessary, in addition to research in related medical fields to combine the influence of lifestyle modifications and modern medicine in order to finally achieve notable improvements in the population's lifespan.

5. Conclusions

Aging is a biological process resulting from a broad accumulation of molecular and cellular damage that leads to a gradual decline in mental and physical capacity and a greater prevalence of pathologies such as cardiovascular and neurodegenerative diseases or cancer, ultimately culminating in the individual's death. Multiple factors have been related to aging, involving intrinsic bases such as genetics and associated genes (APOE, APOC1, FOXO3, IGF1R) and the various epigenetic changes that occur as age advances.

In turn, extrinsic or environmental bases such as nutrition, exercise, disease, and smoking and drinking habits have gained attention due to their influence on aging accelerating processes, which could explain the different aging patterns among individuals. It is clear that numerous discoveries and advances have emerged in the field of gerontology over time, capable of responding to some of the unknowns concerning the bases of aging; however, a long way remains before the complete identification of the aging factor can finally be achieved. For this reason, further research is needed to determine its feasibility and the methods necessary to increase life quality and extend the human lifespan through modifying or decelerating aging-related phenomena.

Author contribution statement

Carla Navarro, Juan Salazar, María P. Díaz, Maricarmen Chacin, Raquel Santeliz, Ivana Vera, Luis D'Marco, Heliana Parra, Mary Carlota Bernal, Ana Castro, Daniel Escalona, Henry García-Pacheco, Valmore Bermúdez: Conceived and designed the analysis; Analyzed and interpreted the data; Contributed analysis tools or data; Wrote the paper.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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