



Factors of the aging process and longevity—selected data

Review

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Abstract

The article presents endogenous and exogenous factors affecting the aging process and longevity, indicating their influence on the epigenome and genome. While discussing endogenous factors, we described genes and protein complexes, metabolic and signaling pathways [IIS (insulin and insulin-like growth factor 1/IGF-1 signaling), ARE/Nrf2 (antioxidant response elements/nuclear factor erythroid-related factor 2), kynurenine/NAD⁺ (nicotinamide adenine dinucleotide and kynurenine signaling)], and the sirtuin enzyme group and antioxidant enzymes (e.g., SOD1).

While characterizing exogenous factors, we indicated the role of nutrition, including the effect of a diet balanced in terms of the number of calories and the effect of consuming polyphenols, including resveratrol, curcumin, or epigallocatechin-3-gallate, and vitamins C and E, as well as the impact of microclimate, stress, the role of physical exercise, and the use of pharmacological agents. Analysis of these data showed that the factors related to the aging process have an influence on longevity and age-related diseases.

Keywords

aging • longevity • endogenous and exogenous factors • epigenome • metabolic pathways

1. Introduction

The 21st century is the era when research into the aging process and life-enhancing conditions started to identify factors that influence human longevity. The above approach is based on health sciences, within which systems biology and biotechnology dominate, with their background of holistic research strategies: epigenomics, genomics, proteomics, and bioinformatics [1, 2, 3, 4, 5, 6]. This era of research also applies to personalized medicine taking into account an individual's response to treatment and differences in gene expression and proteome dynamics, using nanotechnology and targeted therapy, in which substances are delivered directly to the site affected by the disease process [7, 8]. Regenerative medicine, including tissue engineering and cell therapy to treat the effects of disease and accidents, genetic engineering and gene therapy to address the causes of genetic diseases, and anti-aging medicine focusing on "extending" life, are also part of improving quality of life [9, 10, 11, 12, 13]. The above scenario creates a future in which time becomes relative in biological terms. It also fits in with the "evolution" of *Homo sapiens*, leading to the progress of civilization and the growth of the human population, essentially promoting a change in the number of years lived. In the last few decades, life expectancy has doubled in various parts of Asia and Africa, while in North America, Australia, and many European countries, life expectancy has increased by an average of 10 years. It is assumed

that by 2070, human life expectancy will have increased by a further 10 years because, between 1995 and 2020, the average life expectancy in the human population worldwide increased by almost 8 years [14, 15]. It has also been recorded that in countries such as Japan, Switzerland, and Monaco, the lifespan of women is close to 90 years, and it is estimated that the number of people over 65 in these countries will increase more than two times by 2050, and by 2070, the number of people over 90 will increase three times [14, 16]. Although the world's population has increased from around 2.5 billion since the 1950s to over 8.0 billion today and will be much higher than 10 billion in 2055, it is assumed that the number of children, as well as the number of people able to work, will decrease dramatically in the process [14, 17, 18]. It should be noted that although life expectancy has increased significantly over the last 100 years, this has not been accompanied by a sustainable increase in healthy life expectancy [14, 19]. Although biogerontology emphasizes quality of life by adding it to years rather than vice versa, this does not always entail quality of life, where diseases lead to an aging population's burden. At the same time, it should be noted that many studies show that the "capacity" of the economies of individual countries in the coming years, as well as their sustainable development guaranteeing the needs of future generations, will be possible mainly based on current and future generations of young people, created based on increased immigration and family

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fertility [20]. In the context of these data, an important fact is the ever-present deteriorating quality of life resulting from neurodegenerative diseases [Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis], metabolic diseases, cardiovascular diseases, autoimmune diseases, and cancer [21, 22, 11].

2. Factors affecting the aging process and longevity

In defining and characterizing the factors of the aging process affecting longevity in humans, it is important to state that, in terms of physiological phenomena, they are associated with reduced immunity and a significant intensification of inflammation, among other things, due to oxidative stress, including mitochondrial dysfunction, impaired proteostasis, and dysregulation of pathways involved in growth and energy production, leading to deterioration of human health and aging [11]. It has been shown that a low-calorie and balanced diet can have a preventive effect on these processes, which, although protective against pathological conditions associated with human lifespan, is relatively poorly represented in most societies worldwide [23, 24]. It should be noted that the balance achieved as a result of the elimination of conditions leading to, among other things, oxidative processes may significantly affect the rate of aging since homeostasis is affected by age due to changes in the activity of endogenous antioxidant enzymes, leading to damage to molecules, cellular structures, and tissues of the body [25, 26]. On the other hand, the use of excessive doses of exogenous antioxidants that eliminate oxidative states, including vitamins C and E, beta-carotene, coenzyme Q10, lipoic acid, polyphenols, and phytoestrogens, may have toxic effects on the body [25]. Analyzing the contribution of extrinsic factors to aging and longevity, it has been recorded that a calorie-balanced diet reducing insulin and insulin-like growth factor 1 (INS/IGF-1) signalling, extends the lifespan of various animal species [27, 28]. In addition to caloric restriction, the restriction of amino acids such as leucine, isoleucine, and valine, as well as methionine, is also important in extending lifespan and probably has a stronger effect on the aging process than calorie intake alone [29, 30]. Therefore, the amount of protein and the origin and composition of amino acids appear to be more strongly related to the body's metabolism in relation to caloric restriction, which influences health and affects longevity. Dietary restriction of the branched-chain amino acids (leucine, isoleucine, and valine), as well as of methionine and tryptophan, has been shown to extend the lifespan of model organisms significantly, e.g., yeast (*Saccharomyces cerevisiae*), fruit fly (*Drosophila melanogaster*), and nematode (*Caenorhabditis elegans*), as well as mice, rats, and primates [31, 30, 32]. The slowing down the aging process and human longevity, are influenced by all disease prevention activities in the behavioral, dietary and pharmacological areas that modulate the relevant intracellular signaling pathways.

These include not only the previously mentioned low-calorie diet and fasting-mimicking protein restriction diet, but also pharmacological inhibition of the growth hormone (GH) axis, insuline/insulin-like growth factor 1 (INS/IGF-1), the mammalian target of rapamycin-S6 kinase beta-1-phosphoinositide 3-kinase (mTOR-S6K-PI3K) pathway, sirtuin regulation, the use of spermidine and other epigenetic modulators, and pharmacological inhibition of inflammation, including the long-term use of metformin [33]. It should be noted that the latter substance, metformin, discovered in 1922 and introduced as a therapeutic agent in 1957, was designated by the International Diabetes Federation in 2005 as a first-line hypoglycemic drug in type 2 diabetes, which has also attracted increasing attention in recent years as an anti-aging substance [34]. It has been shown that in animals, including humans, metformin is not metabolized and interacts with subunits of the electron transport chain, inhibiting it, with a consequent reduction in the production of adenosine 5'-triphosphate (ATP) [34]. Such a condition thus increases adenosine 5'-diphosphate (ADP) and adenosine 5'-monophosphate (AMP) levels. Although AMP is a substrate for the reduced form of nicotinamide adenine dinucleotide (NAD⁺), involved in the electron transport chain, as well as for the oxidized form of NADH formed in the Krebs cycle, it consequently leads to the activation of AMP-activated protein kinase (AMPK). The latter enzyme inhibits the signaling pathway of the serine/threonine kinase mTOR, which, in higher eukaryotes, is the product of a single gene and is part of two complexes, namely, mTOR1 and mTOR2, which, in effect, regulates metabolic pathways associated with aging and probably delays this process [34, 35, 36]. It must be noted, however, that aging-related action, targeting only metabolic and signaling pathways such as, for example, IIS (insulin and insulin-like growth factor 1/IGF-1 signaling), or other components of the cellular "machinery" such as sirtuins, NAD⁺, Nrf2, and mTOR, without "capturing" the organism as a whole, may hinder the understanding of the effects of dietary, pharmacological, and genetic interventions and thus lead to adverse effects on life extension [37]. Hence, it is pointed out that understanding how metabolic signals are transmitted between organelles, cells, and tissues should open up new possibilities for targeting metabolic regulators locally as targeted therapy. However, this area needs to be better understood to develop and identify modulators of the aging process that will ensure longevity and full health [37]. Inappropriate diet, including hormones in food, and other environmental chemicals and stress have been shown to affect gene methylation and enhance the aging process [38]. Markers characterize this process in humans, among which we distinguish between external indicators, e.g., wrinkles and graying hair, and internal indicators, e.g., changes in telomere length, reduced number of T cells (CD₄ and CD₈), and the epigenetic clock, which seems to be most strongly associated with biological age, as it predicts causes of mortality at a later age

and correlates positively with the physical and mental condition. Despite factual/chronological age, it represents the real/biological age [39, 40]. Hence, it is assumed that the lower the environmental stress in an individual's life resulting from, among other things, nutritional and living conditions (environment), the later oxidative stress occurs in the body (if not to a lesser extent), indicating that the expression level of genes encoding antioxidants is not directly proportional to an individual's age but is mainly related to his or her "quality" of life. In addition to the enormous influence of the environment on the aging process, it has also been shown that eukaryotic organisms have, in the course of evolution, developed genetically conditioned metabolic pathways related to the regulation of lifespan [27, 28]. Studies over the past two decades in model organisms have shown that changes in the transcriptome, which matures with age, are associated with decreased expression of genes encoding mitochondrial and ribosomal proteins, affecting the weakening of the protein synthesis "machinery" [41]. This downregulation of expression is also associated with deregulating immune system genes and constitutive genes relating to stress response and DNA damage [42, 43]. It has been recorded that gene expression, e.g., for ribosomal proteins, decreases with age, whereas the level of degradation of their transcripts initially adjusted to the rate of expression in young organisms is constant and shows no change with age [44]. It implies that the amount of proteins synthesized is reduced precisely because of gene "silencing", but this does not clarify whether this condition applies to all genes/proteins and whether it occurs in all tissues, although gene expression levels have been shown to depend on external factors, i.e., the environment [44]. The opposite direction was noted when analyzing the expression of certain genes in bees, where it was shown to increase with age, and moreover, the level of the juvenile hormone was recorded, accelerating the aging process in these insects [45]. It has also been found that in these insects undergoing reprogramming from collector bees to hive bees, there is a decrease in the level of the juvenile hormone and their rejuvenation, which is associated with a decrease in the expression of the gene of this hormone. At the same time, there is also an increase in the precursor protein vitellogenin, which significantly increases the lifespan of bees [45]. These facts, therefore, indicate that lifespan may also depend on the quality of life, which determines the activity of various genes and their expression, which changes with age, affecting the activity of metabolic pathways modulated precisely by endogenous and exogenous aging factors.

2.1. Endogenous factors in the aging process and longevity

These factors include metabolic/signaling pathways and their genes, transcription factors, protein complexes and enzymes, and genes encoding enzymes related to the antioxidant system. The most important factors include the IIS pathway, the ARE/Nrf2

(antioxidant response elements/nuclear factor erythroid-related factor 2) pathway, the kynurenine/NAD⁺ (nicotinamide adenine dinucleotide and kynurenine signaling) pathway, SIRT enzymes, and the antioxidant enzymes superoxide dismutases (SODs) [46, 47, 48, 49, 50, 51]. It should be noted that signaling in these pathways is modulated by a variety of chemical compounds that act through the epigenetic pathway, including mechanisms of methylation, histone deacetylation, chromatin modeling, and RNA interference (RNAi), which regulates/activates or inhibits the expression of genes encoding signaling pathway proteins, i.e., protein complexes such as IRS, S6K, PI3K, AKT, AMPK, sirtuins, the mTOR complex, ERK (extracellular signal-regulated kinase), and 4E-BP1 (eukaryotic translation initiation factor 4E-binding protein 1) [37, 52].

In characterizing the IIS pathway, it has been shown that its components are hormones such as insulin, IGF-1, and GHs, and their specific receptors, as well as proteins including kinases capable of transmitting the signal and IGF-1-binding proteins [50]. In the case of INS/IGF-1 in the IIS pathway, this is the pathway through which signals are ultimately relayed to the mammalian rapamycin kinase, mTOR, which is mainly a sensor for high amino acid concentrations following prior activation of PI3K or AKT inhibiting FOXO (forkhead box O), which promotes cell growth and aging [53]. It has also been linked to the fact that branched-chain amino acids (leucine, isoleucine, and valine), as well as methionine and tryptophan, and simple sugars and palmitate, affect the signaling pathways described and thus influence more intense aging [32, 50, 54, 55]. Animal protein restriction has also been shown to stimulate the activity of fibroblast growth factor 21 (FGF21), which has no mitogenic properties but is a potent endocrine regulator [3, 11, 56]. It influences glucose and fatty acid metabolism, lowers the levels of low-density lipoproteins, and increases the levels of high-density lipoprotein compounds, thereby contributing, among other things, to weight loss, which is a factor in improving health and prolonging life [57]. The factor FGF21 has also been shown to exert an inhibitory effect on the IIS pathway, while GH and IGF-1 activate the same signal transduction in this pathway as insulin [50, 58].

The second most crucial metabolic pathway associated with aging and longevity is the ARE/Nrf2 pathway, related with cellular protection against oxidative stress elements, providing direct and indirect antioxidant effects [21]. 10. This direct effect of antioxidant elements is linked to the fact that these compounds are active themselves and undergo a redox reaction, which directly neutralizes the elements of oxidative stress, including reactive oxygen species (ROS). On the other hand, their indirect antioxidant action is related to activating the body's natural detoxification systems, causing transcriptional activation of "cytoprotective batteries", that is, proteins that act catalytically [51]. In this ARE/Nrf2 pathway, the Nrf2 factor is a master transcriptional regulator of antioxidant-mediated activity,

which regulates antioxidant genes in response to oxidative stress by binding to their regulatory elements, the AREs, in promoter regions. The genes for catalase (CAT), glutathione peroxidase, SOD, and other antioxidant enzymes have also been shown to be activated by Nrf2 [21, 51]. Studies both *in vitro* and *in vivo* indicate that some flavonoids, such as luteolin, myricetin, and epicatechin, activate the ARE/Nrf2 pathway, which contributes to oxidative homeostasis that may provide a mechanism for chemoprevention of tumorigenesis. However, *in vitro* and at low concentrations (1.5 to 20 μ M), flavonoids may also inhibit the ARE/Nrf2 pathway, facilitating cancer cell growth and proliferation under these conditions [59]. It has also been recorded that with age, the Nrf2 factor activity of this pathway is silenced, and its effects are closely related to the aging process and diseases occurring during this process, as a positive correlation has been shown between Nrf2 activity and lifespan in different animal species [60].

Third among the most important metabolic pathways associated with aging and longevity is the kynurenine/NAD⁺ pathway, which is characterized by the biosynthesis of the NAD⁺ from tryptophan and represents a highly conserved pathway in eukaryotic organisms, from yeast to humans, that plays a significant role in aging in these organisms, including in disease processes [46]. It should be noted that the NAD⁺ factor in this pathway is an essential cofactor in mitochondrial energy production and a cofactor in many enzymatic redox reactions, the amount of which decreases with age, which weakens the cellular defense mechanisms against oxidative stress and predisposes the occurrence of diseases related to the oxidative system, including metabolic and neurodegenerative diseases [61]. In this pathway, the NAD⁺ factor is synthesized anew through the breakdown of tryptophan when the concentration of niacin/vitamin B3 (also known as PP) is insufficient in the body to produce this cofactor, and its inhibition affects the aging process and the occurrence of diseases [61]. Supplementation with NAD⁺ and/or its precursors has been shown to increase longevity in fruit flies, nematodes, and rodents, although it has also been recorded that elevated kynurenine levels in the kynurenine/NAD⁺ pathway increase mortality in humans [62]. The kynurenine/NAD⁺ pathway has been proven to have two main pathways ending in producing the neuroactive metabolite kynurenic acid (KA) or NAD⁺, each active in different tissues and cell types [46, 51]. The functions of NAD⁺ are linked to its role as an enzyme cofactor and as an energy carrier, making its interaction in the kynurenine/NAD⁺ pathway one of the main endogenous factors in the aging process [46]. Other elements among the endogenous factors in aging and longevity are the SIRT enzymes (SIRT1–SIRT7) and antioxidant enzymes; it has been shown that a diet-conditioned change in the activity of the genes encoding these enzymes affects longevity [49]. SIRT1 and SIRT3 have been recorded to promote longevity, as they activate autophagy through deacetylation of its key components, AMPK, and inactivating mTOR [49].

Moreover, polyunsaturated fatty acids (PUFAs) are part of the diet and inactivate PI3K, AKT, and, thus, mTOR. However, it has also been recorded that the longer lifespan of women, relative to men, is conditioned by high plasma levels of sphingomyelin and low levels of triacylglycerols containing just PUFA [63]. It has been demonstrated that the activity of SIRT genes leads to the modulation of organisms' lifespan by regulating signaling pathways, including insulin/IGF 1 signaling, AMPK, and the transcription factors FOXO [64, 65]. The latter FOXO transcription factors are deacetylated in mitochondria by the enzyme SIRT3, while mitochondrial SOD, SOD2, influences greater respiratory efficiency by protecting the body from ROS [50]. It should be noted that FOXO transcription factors also play a significant role in the maintenance of metabolic homeostasis and oxidative balance, including antioxidant activity and stress response, as FOXO1, FOXO2, FOXO6, and especially FOXO3 have been found to strongly influence human longevity [53]. In addition to SIRT enzymes, antioxidant enzymes and SOD in particular, which is associated with both intracellular and extracellular antioxidant systems, are also important components of the endogenous factors of aging and longevity [48]. In humans, within SOD, there is a cytoplasmic dismutase, that is, copper-zinc SOD Cu-Zn (SOD1) encoded by the *hSOD1* gene located in the long stretch of chromosome 21 (21q22.1), the so-called mitochondrial Mn manganese superoxide dismutase SOD2 [*hSOD2*, 6q25.3 (long arm of chromosome 6)], and extracellular superoxide dismutase SOD3 [*hSOD3*, 4q21 (long arm of chromosome 4)] [66, 67]. These three enzymes catalyze the dismutation reaction, i.e., the oxidation of one molecule and the reduction of another, e.g., superoxide anion radical to molecular oxygen and hydrogen peroxide in a two-step reaction: i.e., $\text{SOD Men}^+ + \text{O}_2^- \rightarrow \text{SOD-Me}^{(n-1)+} + \text{O}_2$ and $\text{SOD-Me}^{(n-1)+} + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{SOD-Men}^+ + \text{H}_2\text{O}_2$. This fact substantiates the significant role of the Cu-Zn superoxide dismutase SOD (SOD1); that is, it is found not only in the cytoplasm but also in the cell nucleus, lysosomes, peroxisomes, and, in small amounts, in the intramembrane space of mitochondria [67, 68]. This distribution influences the presence of zinc ions in this enzyme, which determines its high physicochemical stability, as it does not denature easily and retains its activity even at 80°C [69]. It should be noted that a negative fact associated with the SOD1 enzyme is that it undergoes amino acid substitutions due to mutations, thereby creating various abnormal forms of the enzyme that do not fulfill its proper function [70]. It has been shown *in vitro* that mutation of the gene of this enzyme in motor neurons leads to an exchange of His for Cys at position 63 of SOD1, which results in abnormal folding of this protein and lowers its affinity for binding zinc ions, resulting in induction of cell apoptosis [71]. Studies have also shown that abnormal forms of SOD1 resulting from mutations in the *hSOD1* gene are co-responsible for the occurrence of the fatal neurodegenerative disease ALS, known as Lou Gehrig's disease

[72]. The disease typically manifests after the age of 40, is more common in men, and occurs in approximately 2 per 100,000 people worldwide, causing loss of motor neurons in the cerebral cortex and spinal cord, as well as severe muscle weakness, paralysis, and fatal respiratory failure, often within 2–5 years of onset [73]. Despite the degradation of nerve cells, no change in the patient's intellectual state is recorded with the disease, as exemplified by the eminent astrophysicist Professor Stephen Hawking, who battled the disease for more than 50 years [74]. The activity of the SOD gene, *hSOD1*, in humans has been shown to reduce free radical levels in the cytosol, mitochondrial intramembrane space, and peroxisomes [68]. The enzyme SOD1 is also involved in the activation of gene transcription after exposure to oxidative stress, RNA modulation, and regulation of glucose metabolism, and through its association with target of rapamycin complex 1 (TORC1), it is important in the survival of cancer cells in an ischemic environment, as TORC1 is a major mediator of nutrients, a so-called genetic modulator [47].

2.2. Exogenous factors in the aging process and longevity

Exogenous factors in the aging process and longevity include many chemicals, including epigenetic modulators and exogenous antioxidants in the diet, as well as pharmacological agents that inhibit or activate cellular mechanisms, including their metabolic pathways and genes [63]. These factors also include exercise, microclimate, and factors that minimize stress, which affect physical fitness and are strongly correlated with human longevity [75]. It has been recorded in mice that physical activity enables them to live in better health, improves their brain's metabolome, and normalizes neurotransmitter deficits, including acetylcholine, glutamate aspartate, and NAD⁺ [76]. Within the exogenous factors of aging and longevity, special attention should be paid to the diet in which antioxidants play an important role, that is, among others, polyphenols, divided into hydroxybenzoic acids and hydroxycinnamic acids, as well as flavonoids, stilbenes, and lignans found in fruits, vegetables, and beverages [77]. Polyphenols are modulators of microRNAs (miRNAs), i.e., small non-coding RNA molecules having 21 to 22 nucleotides, which affect the expression levels of various genes, including those related to autophagy and mTOR-dependent and longevity-related mechanisms [78]. Among polyphenols, the most important are flavonoids, which, by their actions, are key compounds influencing the aging process and longevity [79]. Polyphenols such as nano curcumin (CUR) or myricetin, among others, are indicated to suppress inflammation by affecting their signaling pathways and, together with genistein, inhibit the signaling pathway NF- κ B (nuclear transcription factor, also known as NF-kappaB or nuclear kappa factor—an enhancer of the light chain of activated B cells), which, as a protein complex, among other things, controls DNA transcription and cytokine production, and promotes AMPK activity and, consequently,

cell survival [80, 81, 82]. Activation of the protein kinase AMPK by AMP and inhibition of mTORC are common mechanisms for many of the metabolic and physiological effects induced by plant polyphenols, as AMPK kinase, as well as mTORC, plays a key role in regulating cell metabolism, autophagy, proteostasis, and cell proliferation and influences the state of the redox response [83]. In addition, activated AMPK, as a regulator of cellular energy homeostasis, is also triggered by, among other things, energy stress signaled by decreased ATP levels and increased AMP levels [85]. AMPK protein kinase also triggers the expression of antioxidant enzymes through the ARE/Nrf2 pathway and, through direct activation of FOXO3, improves proteostasis control and inhibits mTORC [83]. Polyphenols belonging to the exogenous aging and longevity factors have been shown to inhibit the expression of interleukins and suppress ROS production and thus may modulate the function of enzymes such as COX1, COX2, and LOX, which are responsible for increasing oxidative stress in tissues [78, 81]. In addition, a flavonoid such as luteolin reduces, among other things, myocyte apoptosis in post-myocardial infarction states, affecting memory and contributing to increased lifespan [78, 84]. Another important compound among flavonoids is 3-epigallocatechin gallate (EGCG), one of green tea's four main bioactive compounds [82]. EGCG has been recorded to exhibit demethylating properties by acting as a DNA methyltransferase (DNMT) inhibitor in lung cancer, breast cancer, leukemia, and neurodegenerative diseases [78]. In addition, CUR, a potent polyphenolic compound found in vegetables and known primarily for its antioxidant properties, inhibits aging [85]. In contrast, the polyphenol compound resveratrol increases the expression of the hemoxygenase gene, which encodes an enzyme that catalyzes the degradation of haem to biliverdin and bilirubin, iron ions, and carbon monoxide and has an activating effect on AMPK and *SIRT* genes, and induces telomere maintenance through activation of the DNA helicase encoded by *WRN* gene—also called WRN helicase telomerase, without affecting cell proliferation, thus exhibiting, among other things, anti-apoptotic effects [86, 87]. In addition to polyphenols, exogenous antioxidant factors include vitamins and, among them, the most potent antioxidants, hydrophilic vitamin C and hydrophobic vitamin E (tocopherols and tocotrienols, E 306) [26]. Characterizing exogenous factors in the aging process and longevity, it should also be stated that greater expression of genes at a later age encoding antioxidant enzymes and richer supplementation with exogenous antioxidants (in the “right” doses) could theoretically not only extend human life but also contribute to a better quality of life by delaying the occurrence of age-related diseases. Indeed, administration of the polyphenol myricetin, found in red wine, as well as resveratrol, in combination with other antioxidants such as vitamins C and E, has been shown to induce an increased activity of CAT in mouse melanoma cells, while reducing levels of SOD1 [88].

3. Summary

Factors in the aging process and longevity are particularly relevant from the perspective of quality of life in aging societies and the future global population. Complete knowledge and understanding of the structure and mechanisms of the epigenome, genome, transcriptome, and proteome will likely make it possible not only to extend the human lifespan significantly but also to enter a new “era” of medicine, in which the aging process and diseases of this period will be treated even before they occur (proteomics) or after their onset, through activations and/or inactivations, as well as modifications of the relevant genes, making it possible to stimulate stem cells to rebuild and create tissues *in situ*, as well as cloning tissues *in vitro*. It is widely believed that exogenous antioxidants and nutraceuticals, as well as pharmacological agents and epigenetic modulators, can effectively slow down the aging process and protect against disease, thus extending human life, which is linked to, among other things, the activity of various genes, including those related to the intrinsic antioxidant system, whose function weakens with age, leading to the appearance of oxidative stress and the conditions mentioned above [46, 47, 48, 49, 50, 51, 77, 89, 90, 91]. The use of a low-calorie diet in organisms such as nematodes (*C. elegans*), yeast (*S. cerevisiae*), fruit flies (*D. melanogaster*), or rodents (mice and rats), as well as rhesus monkeys (*Macaca mulatta*), led to the identification of candidate genes responsible for aging in these organisms [31, 57, 92, 99]. Studies in humans and laboratory animals have described and identified many mutations of various genes associated with longevity, including more than 200 mutations of the *SOD1* gene, and demonstrated that some of these mutations confer a longer lifespan [70, 93, 94, 95, 96, 97]. It has been recorded that *SOD1* plays a vital role in the antioxidant system, although its mechanism of action and role in aging are still not fully elucidated [98]. It is accepted that antioxidant genes are one of the most critical areas of modern biogerontology, as is diet, which is mainly a diet balanced in terms of calories, carbohydrates, and protein, which significantly determines the rate of aging. Protein restriction and branched-chain amino acid restriction have been shown to substantially affect longevity more than calorie restriction alone [29, 30]. It has been indicated that chemicals such as polyphenols or antioxidants, microclimate, stress minimization, and exercise, as well as pharmacological agents, modulate gene activity and affect various metabolic pathways such as IIS (INS/INS, IGF-1/IGF-1, and GH/IGF-1), ARE/Nrf2, and kynurenine/NAD⁺, as well as sirtuin, *SOD1*, and other enzymes associated with longevity, preventing or delaying the onset of diseases with age [46, 47, 48, 49, 50, 51, 100]. In outlining the factors involved in the aging process and longevity, it is essential to point out that the future of future generations depends on those currently living, not only in terms of what they will leave behind physically but

also probably in terms of what will be written in the program controlling their genes (epigenome). Parental imprinting arises partly from the grandmother’s environment (oocytes develop in a girl’s fetus) and partly from the father’s environment (sperm in a man). However, it is not known how the information transferred from genes at the level of transcription and translation is written initially into them, whether the number of genes is constant in a given species, and by what mechanism genes arise “*de novo*”. Hence, research into the aging process and longevity is about answering the question of how to save what determines “health” and perhaps also “talent” for future generations.

Abbreviations

4E-BP1—eukaryotic translation initiation factor 4E-binding protein 1
 4q21—long arm of chromosome 4
 6q25.3—long arm of chromosome 6
 21q.22.1—long arm of chromosome 21
 ADP—adenozyno-5'-difosforan/adenosine diphosphate
 AKT—also known as PKB (protein kinase B)
 ALS—amyotrophic lateral sclerosis
 AMP—adenozyno-5'-monofosforan/adenosine monophosphate
 AMPK—adenosine monophosphate-activated protein kinase
 ARE/Nrf2—antioxidant response elements/nuclear factor erythroid-related factor 2
 ATP—adenozyno-5'-trifosforan/adenosine triphosphate
 CAT—catalase
 COX1—cyclooxygenase 1
 COX2—cyclooxygenase 2
 CUR—curcumin
 DNMT—DNA methyltransferase
 E 306—vitamin E
 EGCG—3-epigallocatechin gallate
 ERK—extracellular signal-regulated kinase
 FGF21—fibroblast growth factor 21
 FOXO—forkhead box O transcription factor
 GH—growth hormone
 GH/IGF-1—growth hormone/insulin-like growth factor 1
 hSOD1—human gene of superoxide dismutase 1
 hSOD2—human gene of superoxide dismutase 2
 hSOD3—human gene of superoxide dismutase 3
 IDF—International Diabetes Federation
 IGF-1—insulin-like growth factor 1
 IIS—insulin and insulin-like growth factor 1/IGF-1 signaling
 INS/IGF-1—insulin and insulin-like growth factor 1
 IRS—insulin receptor substrate 1
 KA—kynurenic acid
 LOX—lipooxygenase
 miRNA—microRNA
 mTOR—mammalian target of rapamycin
 mTOR1—mammalian target of rapamycin 1

mTOR2—mammalian target of rapamycin 2
 mTOR-S6K-PI3K—mammalian target of rapamycin-S6 kinase
 beta-1-phosphoinositide 3-kinase
 NAD⁺—nicotinamide adenine dinucleotide
 NF-κB—nuclear factor kappa-light-chain-enhancer of activated
 B cells
 Nrf2—nuclear factor erythroid-related factor 2
 PI3K—phosphoinositide 3-kinase
 PUFA—polyunsaturated fatty acid
 RNAi—RNA interference
 ROS—reactive oxygen species
 S6K—S6 kinase beta-1
 SIRT—sirtuin
 SOD—superoxide dismutase
 SOD1—cytoplasmic superoxide dismutase 1
 SOD2—mitochondrial superoxide dismutase 2
 SOD3—extracellular superoxide dismutase 3 kynurenine/NAD⁺
 pathway—kynurenine signaling/nicotinamide adenine dinucle-
 otide pathway
 TORC1—target of rapamycin complex 1
 WRN—Werner syndrome
 WRN helicase—Werner syndrome ATP-dependent helicase.

Authors' contribution

D.S.—Concept, acquisition of data, data analysis and interpretation, writing—original draft preparation, and literature review. B.T-D.—Supervising the project, writing—review and editing, visualization, final proofreading and approval of the version for publication, and funding acquisition. W.D.—Concept, supervising the project, writing—review and editing, data analysis and interpretation, literature review, visualization, final proofreading, and approval of the version for publication.

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Conflict of interest

The authors have no potential conflicts of interest to declare.

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