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Review article

Stabilization of telomere by the antioxidant property of polyphenols: Anti-aging potential

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ABSTRACT

Aging is a form of a gradual loss of physiological integrity that results in impaired cellular function and ultimately increased vulnerability to disease and death. This process is a significant risk factor for critical age-related disorders such as cancer, diabetes, cardiovascular disease, and neurological conditions. Several mechanisms contribute to aging, most notably progressive telomeres shortening, which can be counteracted by telomerase enzyme activity and increasing in this enzyme activity associated with partly delaying the onset of aging. Individual behaviors and environmental factors such as nutrition affect the life-span by impact the telomerase activity rate. Healthy eating habits, including antioxidant intakes, such as polyphenols, can have a positive effect on telomere length by this mechanism. In this review, after studying the underlying mechanisms of aging and understanding the relationships between telomeres, telomerase, and aging, it has been attempted to explain the effect of polyphenols on reversing the oxidative stress and aging process.

1. Introduction

Aging is a gradual time-dependent physiological deterioration that results in an increased risk of cell death or outbreaks [1]. Contrary to contagious diseases, the prevalence of age-related degenerative disorders is growing exponentially worldwide [2]. Heart disease, cancer, chronic lower respiratory disease, neurodegenerative disorders, stroke, and hypertension are the leading cause of mortality among age-related death [3]. Various factors are involved in the occurrence of aging, including genomic instability, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, cellular senescence, altered intercellular communication, and Telomere shortening [4]. Telomeres are the physical terminals of linear chromosomes that consist of a non-coding sequence that stabilizes the genome by keeping the chromosome end free from fracture and proximity [5,6]. In each cell division, telomeres lose some of their lengths. The shorter the telomeres, the older the cells become, leading to disease and cell death [7]. A ribonucleoprotein enzyme named telomerase that has DNA polymerase activity and by using an RNA component as the template could synthesize telomeric repeats at chromosome ends, which subsequently prevents this chromosomal shortening. Telomerase is actively present in stem cells, and potentially in all cells, and if its activity increases, chromosomal shortening will be delayed [8].

Various external factors, including lifestyle, Nutrition intake, genetic mutation, and heredity, can contribute to senescence [9]. Studies of twins have shown that only 20–30% of life-span depends on genetics, while the majority of it depends on individual behaviors and environmental factors [10]. Some habits in life, such as smoking, exposure to pollution, low physical activity, psychological strain, and unhealthy diets, can dramatically increase oxidative stress. Telomere shortening and, as a result, the aging process accelerate due to oxidative stress [11]. Some age-related diseases such as obesity, cardiovascular disease, and insulin resistance are associated with increased oxidative stress and

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inflammation and decreased telomere length and telomerase activity [12].

The dietary pattern can influence telomerase activity and lead to slow telomere length shortening, which is a crucial factor in postponing aging. Polyphenols are found in fruits and vegetables and represent an extended group with more than eight thousand identified compounds. Polyphenols have been shown to exert beneficial effects on many age-related diseases, which affect telomeres length [13]. The structure of polyphenols contains an aromatic ring with at least one hydroxyl group attached to it, polyphenols have been categorized into four major groups (phenolic acids, Flavonoids, Stilbenes, and Lignans) based on source, origin, biological functions and chemical structures [14,15]. There is Convincing evidence suggesting that polyphenols can enhance cellular antioxidant defense and subsequently raise protective impact against age-related disorders [16]. Various compounds of the polyphenol group, act as potent antioxidants in vitro and in vivo [17] and prevent oxidative stress damages [18]. With affecting different AMPK [19], PI 3-k/AKT [20], NF-κB [21] signaling pathways, they can maintain their anti-aging activity by extending life-span. The relationship between apoptosis with polyphenolic compounds has also been confirmed to be the main target for increasing life expectancy [22,23]. Studies reviewed in this article have shown that by modifying lifestyle, eating low-fat diets enriched with polyphenols, regular physical activity, and reducing stress, telomere lengths in blood cells increase significantly.

2. Aging: molecular mechanisms

Aging is one of the time-dependent physiological events that occur sooner or later in all living cells. Gradual changes in aging can impair the physiological function of the cell and ultimately increase the susceptibility to death [24]. This subversion is the primary risk factor for major human pathologies, including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Various factors are involved in the occurrence of aging, including genomic instability, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, cellular senescence, and altered intercellular communication, and Telomere shortening [4]. In this section, we will give a brief overview of the factors affecting aging.

One of the most critical factors in aging is the accumulation of genetic damages throughout life. DNA stability is compromised invariably by exogenous factors such as physical, chemical, and biological damages [25]. As well DNA integrity is at risk by endogenous factors such as unrepaired errors in replication (point mutations, translocations, chromosomal gains, and losses), telomere shortening, and activity of reactive oxygen species (ROS) [26]. Damages caused by exogenous and endogenous factors, including base damage, adduct formation, inter-strand cross-link, spindle errors, double-strand break, and miss-match of bases, accumulate randomly over time and causes aging [4].

Another molecular mechanism that induces the aging process is epigenetic alteration. Some of the epigenetic changes are DNA methylation, histones modification, and chromatin remodeling [27]. Aberrant DNA methylation, increased histone H4K16 acetylation, H4K20 trimethylation, or H3K4 trimethylation, as well as decreased H3K9 methylation or H3K27 trimethylation and also decreased level of HP1α and NuRD in the chromatin remodeling process is the most critical epigenetic alterations that increase transcriptional noise, impaired DNA repair system, and chromosomal instability [4]. An increase in transcriptional noise and aberrant production of many mRNAs are the inducing factors of aging. For instance, non-coding RNAs (gero-miRs) impact life-span by aiming mechanisms of longevity or by modifying stem cell behavior that is associated with the aging process [28,29]. Histone demethylation targets the insulin/IGF-1 signaling pathway, one of the most important pathways in cell aging that modulates life span [30].

The other molecular mechanism that induces senescence is impaired protein homeostasis or "proteostasis" [31]. Proteostasis is a network of quality-control processes comprised of protein clearance mechanisms that inhibit the toxicity of misfolded proteins. Some of these cell quality control mechanisms are macro-autophagy, chaperone-mediated autophagy, proteasomal degradation, and chaperon mediated folding [4]. One of these proteotoxicity regulators is MOAG-4 that prevents age-related misfolded proteins aggregate independently of molecular chaperones and proteasomes [32]. Failure to destroy the unfold proteins by proteostasis system will result in the accumulation and aggregation of these proteins and eventually induce aging [33]. In various aging related pathological conditions, such as neurological disorders, it has been shown that the capacity of the proteostasis network decreases with age. Misfolded protein aggregate deposits in amyloid- like fibrillar are now generally accepted as hallmarks of many neurodegenerative diseases and other mostly age- dependent pathologies, such as type II diabetes [34].

Another molecular mechanism that cause aging is related to metabolic alteration and deregulated nutrient sensing [35]. One of the metabolic pathways that induce aging is insulin and insulin-like growth factor (IGF-1) signaling (IIS) pathway. IGF-1 formed in response to GH and hyperglycemia. IGF-1 induces the PI3K-AKT signaling pathway that eventually leads to the aging process by increasing the mTOR factor. Besides, the PI3K-AKT signaling pathway is an inhibitor of the FOXO factor, which is an inhibitor of the aging process. Thus AKT controls the aging process by inducing mTOR and reducing FOXO. Genetic polymorphisms or mutations that reduce the functions of GH, IGF-1 receptor, insulin receptor or downstream intracellular factors such as AKT, mTOR, and FOXO, have been linked to longevity [4,36]. Activation of the mTOR signaling pathway increases the rate of aging and animal model studies showed that the use of mTOR inhibitors delay life-span and has a protective effect against most of the major age-related diseases [37]. This mechanism is one of the best-characterized pathways of life-span IIS signaling pathway acts as a double-edged sword, sometimes in favor of aging and sometimes opposed to it [38]. It has been observed that in normal cells with senescence or in cells with premature aging, the levels of GH and IGF-1 are decreased, whereas the reduction of IIS extends longevity [39]. Decrease of IIS is a defense response against physiological or pathological aging. It is as if cells reduce the rates of growth, cellular damage, and metabolism for more prolonged survival and extend their life-span. However, low levels of IIS signaling are in contrast with life, and this defense mechanism may be the cause of erosion and aging [40]. Another related molecular mechanism that induces chronological senescence is the accumulation of non-telomeric DNA damage and de-repression of the INK4/ARF locus [41].

In the meantime, the amount of senescent cells increases with aging, reducing the cleansing power of these cells is also another factor should to be considered. Decreasing the potency of the immune system and its ability to effective phagocytosis and clearance are among the contributing factors in aging [42]. Senescence of a cell is said to be a useful compensatory response in removing damaged cells and oncogenic cells from tissues, provided availability of an efficient cell replacement system that involves the clearance of senescent cells, and mobilization of progenitors to re-establish cell numbers. Sporadic damage in young cells leads to cellular senescence. The responses of the immature cells to cellular senescence are tissue homeostasis and blocking the proliferation of damaged cells. This response is an anti-aging and anti-cancer activity performed by the immature cells. However, in the old cells, the accumulation of damages and decreased levels of clearance, repair, and cell regeneration are the causes of cellular senescence. The responses of old cells to these lesions are decreasing tissue function, increasing inflammation, the effect on adjacent cells, and exhaustion of stem cells, which eventually leads to the induction of aging.

Nevertheless, in these cells, cellular senescence contributes to the anti-cancer activity by blocking the proliferation of damaged cells [4].

The aging process is associated with variations in intercellular communication such as endocrine, neuroendocrine, or neuronal [43]. In aging cells, neurohormonal signaling pathways, such as renin-angiotensin, adrenergic and insulin-IGF1 signaling are not regulated due to the increase of inflammatory reactions and immune responses. In this way, the intracellular and extracellular homeostasis is altered and will have a negative effect on the functional properties of all surrounding tissues [4,44]. One of the fundamental hallmarks that reinforces the aging process is an age-associated inflammation. This type of molecular mechanism inhibits epidermal stem cell function and fails the adaptive immune system. Also, inflammatory cytokines prompt aging in neighboring cells via gap junction [45–47].

Triggering programmed cell death (apoptosis) is an effective mechanism to prevent cellular aging. In the process of apoptosis, older cells are destroyed and replaced with young cells. However, this defense against aging has many risks. Harmful Mutations that occur each time as cells divide is a predisposing factor in cancer. In addition, each cell divides at a certain number of times, and after 50–80 times due to shortening, the telomere length cell becomes replicative aging. Shortening the telomere length harms health and leads to genomic instability and jeopardizes the function of the cell cycle consequently, the cells enter the aging and apoptotic phases [48–50]. In this case, the cells use an enzyme called telomerase to delay the process of telomere shortening. This will be discussed in more detail below.

3. Telomeres and telomerase biology

A telomere is a repetitive nucleotide sequence at the end of the chromosome that preserves chromosome degradation and prevents chromosome fusion [48]. The telomeres in vertebrates consist of a double-stranded and single-stranded region [51]. The single-stranded telomere region has a TTAGG sequence that has been repeated nearly 2500 times in humans [52]. The double-stranded ends of telomeres may be known as double-strand breaks and can be attacked by the unwanted repair system. The six-part shelterin protein complex is bound to telomeres and forms the T-loop 3D structure for more protection and integrity increase [53]. Another structure that helps to maintain the integrity of the chromosomal end is a sophisticated secondary structure called G-quadruplex (G4) [54].

At birth, telomere length is about 15,000 base pairs and gradually reaches 4000 base pairs among the elderly [55,56]. During each replication, the length of chromosomes becomes shorter because a segment of the chromosome's end does not replicate [57]. Shortening the telomere length adversely affects health and leads to genomic instability and jeopardizes the function of the cell cycle; hence, the cells enter the aging and apoptotic phases [48].

Telomere shortening gets resolved by a ribonucleoprotein enzyme called telomerase. Telomerase is consisting of two components: telomerase reverse transcriptase protein (TERT) and telomerase RNA component (TERC), which contains the template for telomeric repeat sequence [58]. Telomerase activity is regulated in all tissues and is usually expressed only during embryogenesis. Except for proliferating organs such as skin, intestine, bone marrow, dividing lymphocytes, ovaries, and testes, telomerase activity is significantly suppressed after birth due to loss of TERT gene expression [59,60]. Lack of telomerase activity in most human somatic cells results in telomere shortening during aging. Furthermore, overexpression of TERT, and a highly increased amount of the telomerase enzyme in the cells can result in cell immortalization [61].

4. Polyphenols: novel prophylaxis agent in the aging process

Polyphenols are chemical compounds, rich in phytochemicals that are commonly found in plants. Polyphenol-rich dietary sources such as fruits (grapes, apples, pears, cherries, berries), tea, coffee, red wine, cereals, dry beans, and chocolate, can act as potent antioxidants [62,63]. These compounds have been shown to induce the overexpression of antioxidant enzymes such as superoxide dismutase and catalase [64]. Studies have demonstrated that polyphenols provide economic and health advantages and reduce diseases [65]. Over the past centuries, epidemiological studies of polyphenols have attracted the attention of nutrition scientists, and these compounds can play a vital role in human health and preventing a variety of diseases [66]. Especially in aging, it is a natural process; changes can occur in any part of the body over time, which reduces the efficiency of the body and promotes the development of various diseases [67,68]. Recent studies have shown a series of phenomena that play a crucial role in the aging process, including oxidative stress [69]. Oxidative stress plays a role in disrupting the balance between the production of free radicals and the antioxidant defense system, paving the way for a variety of pathological diseases such as cardiovascular disease, insulin resistance, and metabolic syndrome. Antioxidants can be both synthesized in the body and absorbed through the diet [70,71]. Polyphenol-rich diets are potent antioxidants that function in vitro and in vivo, referred to in Fig. 1 [72]. Thus polyphenol compounds such as resveratrol, quercetin, and curcumin have a protective role against oxidative stress injuries as a novel therapeutic potential with anti-aging activity; it reduces various diseases and increases life-span [73].

Extended longevity is achieved through various transport paths, including AMPK (AMP-Activated Protein Kinase). AMPK is a serine-threonine kinase that is activated by phosphorylation of threonine. By activating this kinase, many downstream substrates, including anabolic and ATP-consuming pathways such as fatty acid and cholesterol production, which are not required for short-term survival, are also inhibited. It activates many catabolic and ATP-producing pathways such as glucose translocation, glycolysis, and fatty acid oxidation, as well as modifying gene expression and protein synthesis. This process results in the maintenance of autophagy and mitochondrial function. Autophagy leads to hemostasis by removing old and damaged organelles [19,74]. In addition, the polyphenolic compounds can enhance the autophagy effect by modifying various message delivery pathways, including phosphoinositide 3 -kinase (PI3-k)/AKT, mammalian target of rapamycin (mTOR). These signaling pathways affect the processes of proliferation, cell differentiation, apoptosis, angiogenesis, and metastasis, leading to cancer if these pathways are not up-regulated [20,75]. Also, Phenolics (especially resveratrol) activate genes known as sirtuins, which can be expressed independently of other pathways (such as mTOR) [76]. Sirtuins may provide some benefits, including extending life-span, increasing protein stability(deacetylation), gene stability after DNA breaks, and calorie restriction [77]. Calorie restriction has been recognized as a new treatment to reduce common diseases such as aging and neurological disorders and type 2 diabetes [78,79].

Other essential changes in the aging process include chronic inflammation of the body's cytokines (such as interleukin (IL)-6, tumor necrosis factor (TNF)-α). Inflammation arising from the aging process is defined at the cellular, molecular, and systemic levels [80]. The nuclear factor NF-KB signaling pathway plays a crucial role in the inflammation process, which its activation has been observed in the skin, kidney, heart muscle, and brain [81–83]. NF-κB signaling causes hypothalamic inflammation and dysfunction of the entire body's immune system, especially impaired endocrine regulation of glucose and lipid metabolism [84].

Anti-inflammatory activity of polyphenolic compounds such as apigenin, catechin, ellagic acid, luteoloside, and rutin, has been observed in acute and chronic inflammation [85]. The molecular mechanisms of polyphenolic compounds are correlated with inhibiting NF-KB pathways [86]. hence, the lack of polyphenolic compounds leads to other disorders such as atherosclerosis, diabetes, obesity, sarcopenia, and

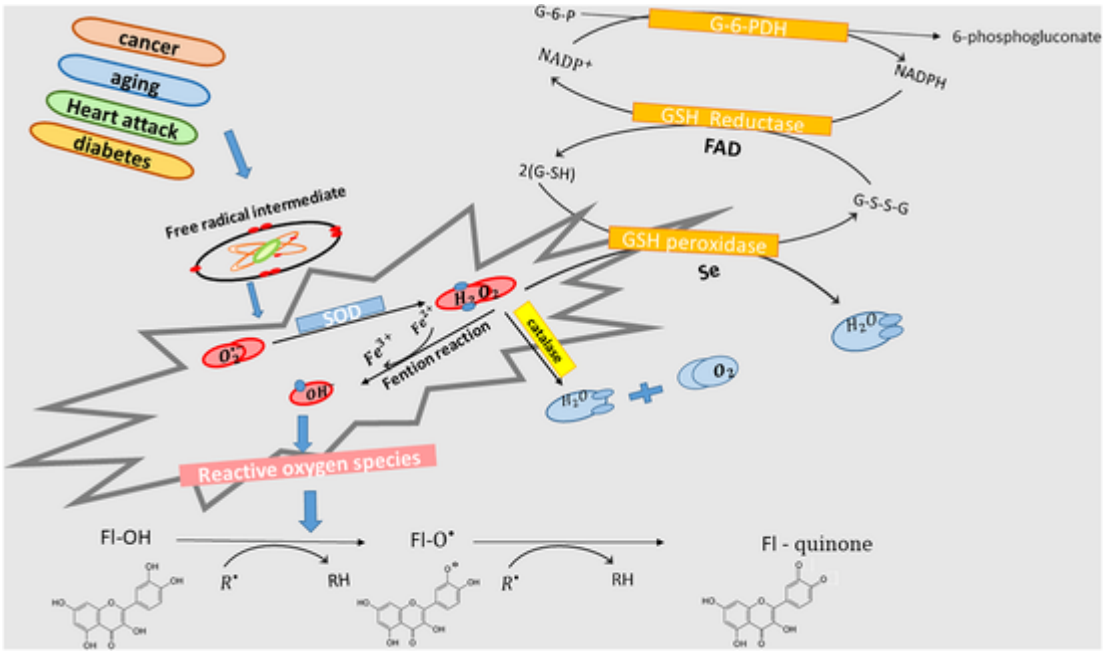

Fig. 1. An imbalance between free radicals and antioxidants can interfere with body redox and oxidation and body reactions, leading to tissue damage such as cancer, diabetes, aging, heart attacks, and other problems. Antioxidants are the body's defense mechanisms against oxidants. Catalase, glutathione peroxidase, and glutathione reductase are the most common antioxidant enzymes. One of the processes of chemical oxidation is the Fenton reaction in which an iron ion acts as a catalyst in an acidic environment and Reacts with oxidants and produces radical hydroxyl. The most important oxidant can be reactive oxygen species (ROS).ROS is a term defining some free radical and reactive molecules which are derived from molecular oxygen. Polyphenols are flavonoid compounds that can act as potent antioxidants and donate a hydrogen atom of the hydroxyl group to the free radical oxygen. During this process flavonoid phenoxyl radical (FPR) and a stable molecule (RH) are formed. FPR may react with the second radical and create a stable quinone structure.

Alzheimer's disease [20]. Obesity is a major problem that releases inflammatory cytokines from adipose tissue, which increases the risk of other metabolic diseases [66]. Calorie restriction is an excellent way to reduce obesity and enhance memory in which polyphenols have similar effects [87,88]. Polyphenols perform the anti-obesity activity by inhibiting or reducing lipid synthesis in adipocytes, modulating lipogenesis, reducing inflammation and oxidative stress, activating AMPK through inhibiting ATP production [89,90]. Apoptosis is a natural cellular event that plays a vital role in the evolution, immune system, and natural life of the cellular organisms [91]. Autophagic processes also lead to apoptosis [92]. During aging, inadequate cell death causes cancer to spread, and excessive cell death leads to tissue atrophy, associated with reduced life-span [93]. Polyphenolic compounds can inhibit muscle atrophy and damage to the immune system from preventing the apoptosis process while enhancing this process is effective in clearing cancer cells. There is a great deal of controversy regarding the ability of these compounds to promote or reverse apoptosis. In addition, the relationship between apoptosis and the aging process needs further studies and clarification [75,94,95].

The studies have identified the genes that can extend life expectancy and reduce age-related diseases, including the Klotho gene. Polyphenols can influence intracellular function through activation of the Klotho gene, which induces the transcription factors, insulin-like growth factor 1 (IGF-1), and transforming growth factor (TGF-1β) [23]. The mechanisms mentioned above are generally outlined in Fig. 2.

Researchers around the world are currently working hard to rejuvenate old cells to reverse the aging process. Age-related diseases such as cancer, diabetes, and dementia are each a unique cause. Epidemiological and laboratory evidence suggest that polyphenol-rich diets play a vital role in the prevention and treatment of age-related diseases. They also have positive effects on mental and physical health. The use of these compounds and their association with increased life expectancy as a new treatment in the aging process is under investigation; growing evidence suggests that polyphenol-rich diets could be reversing the aging process in the new generations.

5. The importance of telomerase in aging

Aging is a natural process that gradually reduces physiological functions, which leads to increased vulnerability to disease and, ultimately to death [96]. Aging is a universal process in which many mechanisms are involved. Cellular aging is a type of stress response that is a significant contributor to age-associated tissue dysfunction, reduced degenerative capacity, and diseases. In the year 1961, Hayflick et al. considered three phenotypes for aging, including normal aging, accelerated aging and successful aging [97,98]. Identical studies on twins have shown that only 20–30% of a person's life-span is related to genetics and the most critical factor contributing to a healthy life is appropriate nutrition and lifestyle [99,100].

Many of these Research Perspectives underlie nutrition, lifestyle, and longevity as modulations of telomere length [101]. Telomeres are specialized structures composed of TTAGGG tandem repeats at the end of eukaryotic chromosomes that resemble those of plastic tips on shoelaces. The function of these tips is to protect the fusion and break down of chromosomes and suppressing the activation of DNA damage response (DDR) [101,102]. At each cell division, Due to the end-replication problem, telomere lengths get shorter and it is accelerated by many other factors, such as oxidative stress, replication stress, and inflammation [11].

Short and dysfunctional telomeres can be repaired by the telomerase enzyme. As mentioned in the preceding sections, the telomerase enzyme is composed of two subunits; TERT and TERC, which inhibit telomere shortening by adding repeat telomeric sequences to the end of the chromosome [103]. Human TERC (hTERC) is expressed in stem cells and telomerase-positive cells but is suppressed shortly before birth in somatic cells [104,105]. Mutation in the hTERC gene leads to autosomal dominant dyskeratosis congenital. Premature aging traits such as grey hair, dental loss, bone marrow failure, cirrhosis, lung disease, and skin cancer have been observed in these patients [106,107]. Blackburn, Greider and Szostak in 2009, received the Nobel Prize for the dis-

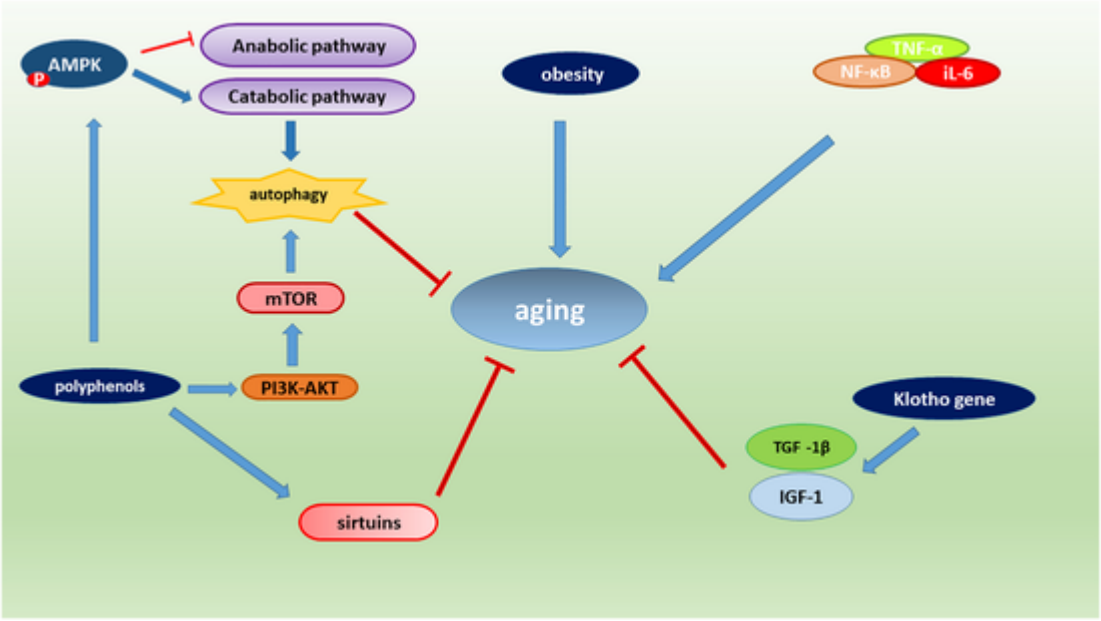

Fig. 2. Schematic image of signaling pathways that enhance or weaken aging.AMPK-dependent kinase, as the main regulator of the cell, plays a major role in activating catabolic and anabolic pathways, in which polyphenolic compounds have a prominent role in enhancing phosphorylation of these pathways and activating downstream signals. These compounds enhance autophagic processes by affecting other signals such as (PI3-k)/AKT, and along with the expression of sirtuins and klotho genes, cytokines and weight loss, play their anti-aging activity.

covery of "how chromosomes are protected by telomeres and the enzyme telomerase". This theory, which delayed telomerase activation by postponing telomere erosion and aging, had a major impact on the scientific community [101].

The small molecule TA-65 is a compound extracted from Astragalus mem-branaceus, which is the telomerase activator in-vitro and in-vivo [108]. TA-65 increases telomere lengths and decreases the percentage of critically short telomeres as well as DNA damage foci both in-vitro and in-vivo. In fact, dietary supplementation of TA-65 in mice leads to an improvement in several health-span indicators such as glucose tolerance, osteoporosis, and skin fitness, without significantly increasing the cancer incidence [109]. A study of healthy elderly volunteers taking TA-65 supplements showed a significant improvement in the cardiovascular system, metabolism, bone mineral density, and immune system [110].

In 2019, Kokubun and colleagues conducted a study on telomerase activity in ischemia. In the ischemic muscles of old mice, the levels of reactive oxygen species (ROS), DNA double-strand breaks, and expression of p53, p16, and Bax/Bcl-2 were augmented, and expression of HIF1α/vascular endothelial growth factor (VEGF) and PGC1α were diminished. The results were in contrast to young mice and mice treated with TA-65. Collateral growth under ischemic conditions is impaired in aged animals due to low telomerase activity, increased ROS, resultant DNA damage, and expression of tumor suppressor and pro-apoptotic proteins. These data suggest that telomerase activation enhances collateral growth and preserves ischemic tissue in old individuals [111]. The expression of telomerase enzyme in transgenic mice was investigated in a study, and the effects of rejuvenation in tissue fitness were observed in these mice. Interestingly, transgenic mice with cancer-resistant backgrounds had reduced abnormalities and increased life expectancy by 43% [112,113].

Furthermore, another study showed that reactivation of telomerase by increasing the level of TERT in adult or old mice using adenovirus resulted in a significant increase in telomere length without increasing vulnerability to cancer. In this study 1- and 2-year old mice were treated with an adeno-associated virus (AAV). This intervention with AAV increases the expression of TERT genes and has beneficial effects on health, including insulin sensitivity, osteoporosis, neuromuscular coordination, and several molecular biomarkers of aging. The results of this study showed that with this telomerase gene therapy, the median life-span of 1-year-old and 2-year-old mice increased 24 and 13%, respectively. This study illustrates the role of TERT in delaying physiological aging and extending longevity in normal mice through a telomerase-based treatment and demonstrates the feasibility of anti-aging gene therapy [114].

Klotho (KL) is an anti-aging protein that is mostly produced in the kidney and secreted into the systemic circulation. The study showed that during aging, production and secretion of KL proteins decreases, and the subsequent risk of age-related diseases increases. This study suggests that both KL and telomeres regulate the aging process in stem cells with the help of telomerase subunits include TERF1, POT1, and TERT using the TGF-ß, Insulin, and Wnt signaling. Therefore, it can be concluded that this protein has an active role in regulating longevity through the action of the telomerase enzyme [115].

Recent studies have pointed to the anti-aging properties of telomerase and have shown that telomerase can extend shorter telomeres and protect taller telomeres to ensure stability. It seems like a way to turn back the biological clock. So by activating telomerase through specific diets such as polyphenols, we may maximize life expectancy and reduce age-related diseases (Table 1).

6. Targeting telomeres by polyphenols in the aging process

Levels of oxidative stress, inflammation, mitochondrial dysfunction, antioxidants, shortening of telomeres, and gene mutations all have a crucial role in determining cellular aging [116]. Telomeres are the physical terminals of linear chromosomes that keep the chromosome end free from fracture and proximity [5,6]. In each cell division, telomeres lose some of their lengths [7]. Evidence suggests that oxidative stress and the free radicals produced by it play an essential role in telomere shortening through decreasing the activity of telomerase or TRF-2 level [117].

However, aging can be delayed by activation of the telomerase enzyme, which acts as a reverse transcriptase enzyme and adds nucleotides to the end of the chromosome, thereby decelerates the aging

Table 1
Studies on avoiding telomere shortening by increasing telomerase activity.

Author	Aim	Outcome	Ref
Tomás-Loba A et al.	Increased expression of Telomerase *reverse transcriptase* (TERT) in cancer resistant transgenic mice using enhanced expression P53,P16,P19ARE	Overexpression of TERT has anti-aging activity.	[151]
Ornish D et al.	Measurement of telomerase activity by diet and lifestyle changes in men with prostate cancer in PBMCs during three months	% 30 telomerase activity in PBMCs increased with increased physical activity and low-fat diet	[152]
de Jesus et al.	Use of TA-65 as a telomerase activator in the diet of female mice	Increases the level of reverse transcriptase telomerase	[153]
de Jesus et al.	Effects of Telomerase gene therapy in adult (1 year) and older (2 years) mice using adeno associated virus	Adult and older mice had telomere lengths of 1 and 2%, respectively and emphasis on the anti-aging role of telomerase	[154]
Boccardi V et al.	Evaluation of the relationship between telomere length (LTL) and telomerase activity in older adults using the Mediterranean diet (MD).	High telomerase activity and positive telomere length change in people using the Mediterranean diet	[155]
Ullah M et al.	Increased KL gene expression and its association with telomerase activity.	KL gene enhances expression of TERT and $TERF_2$ and It is involved in regulating telomere length and telomerase activity and extending lifespan	[156]
Kokubun T et al.	Treatment of old mice with ischemia by TA-65	Activation of telomerase increases the collateral growth in these patients and saves the ischemia tissue of the elderly.	[157]
Epel ES et al.	Evaluation of telomere shortening acceleration in response to life stress	In healthy women under high physiological stress, accelerated cellular senescence such as, telomere shortening, telomerase,oxidative stress depletion were observed in PBMC.	[158]
Vujkovac AC et al.	Telomere length and telomerase activity and aging in Fabry disease	In people with Fabry, telomere length is shorter but telomerase activity is higher than in the healthy group, leading to premature aging.	[159]
Cen J et al	Evaluation of the anti-aging effect of estrogen on telomerase activity in ovariectomized rats - Animal model of menopause	Exogenous estrogen can significantly up-regulate telomerase activity and TERT mRNA expression to exert the effects of anti-aging.	[160]
Yip BW et al.	Sex-dependent telomere shortening, telomerase activity and oxidative damage in marine medaka Oryzias melastigma during aging	Results showed that telomere shortening as a biomarker of aging and accelerated aging in marine medaka/fish.	[161]
Fathi E et al.	Effect of zinc sulfate on adipose-derived mesenchymal stem cells exposed to low frequency magnetic field and its relation to telomere length.	It seems that ZnSO4 may be a beneficial agent to delay aging of ELF-EMF-exposed MSCs due to the induction of TERT gene expression	[162]
Arsenis NC et al.	The relationship between physical activity on telomere length	Physical activity and exercise can have a protective and restorative effect on telomere length, resulting in longer life spans.	[163]

All of the studies show that by increasing telomerase activity through gene expression or dietary supplements, telomere shortening will be avoided, which increases life expectancy and improves quality of life.

process [118]. Despite the oxidative stress and inflammation in the cancer cells, telomerase is highly expressed, and telomeres are not shortened due to reactivation of the hTERT gene, which is generally silent in adult tissues [119]. Inhibition of oxidative stress protects telomerase activity in healthy cells but suppresses its activity in tumor cells. This apparent contradiction has been accounted for by the higher redox homeostasis threshold that exists in cancer cells, causing them to have a high demand for reactive oxygen species (ROS) [120].

The effects of inflammation and oxidative stress on telomere length regulation are discussed below. In a case-control study, it was shown that in patients with periodontitis, increased oxidative stress and inflammation lead to shortening of telomere length [121]. Also, in patients with Parkinson's who have progressive oxidative stress, telomere length in blood cells is shortened [122]. Moreover, it has been shown that telomere length is reduced in diabetes type I and II by increasing oxidative stress, and in the elderly with obesity and insulin resistance, leukocytes had shorter telomere length [123]. Another study on aging showed that older adults living in Greece had lower oxidative stress and higher antioxidant levels than elderly Dutchmen. This population study showed that elderly Greek men consume an antioxidant-rich diet, and their telomere length was significantly longer. This study demonstrates a direct relationship between increased oxidative stress and decreased telomere length in the elderly [124].

Besides oxidative stress, inflammation, and inflammatory factors such as TNF-alpha, IL-6, and IFN-gamma in circulating macrophages, play an essential role in the shortening of telomeres and the onset of senescence [125]. Also, mutations in TERC and TERT increase pro-inflammatory cytokines in the lung and cause premature aging in alveolar stem cells. These results indicate the relationship between inflammation and telomere shortening [126].

The correlation between some mechanisms related to oxidative stress and telomere length are discussed below. Telomere length gets reduced through various mechanisms such as inadequate nutrition. Reducing calories leads to decreased energy metabolism and increased ROS production, one of the most important factors in the formation of oxidative stress [127]. Overproduction of ROS leads to the oxidation of biological molecules such as lipid, protein and mitochondrial DNA and genomes such as telomeres over time [128]. In addition, telomere shortening induces P53 activation, which leads to mitochondrial dysfunction. That mitochondrial dysfunctional renews genomic and mitochondrial DNA damage and stress DNA disorder, which is associated with loss of structure and the DNA information, and it is irreversible [129]. DNA damage is associated with inhibition of telomerase [130] (Fig. 3).

Another mechanism by which oxidative stress can cause telomere shortening is defective endonuclease III-like protein 1 (Nth1), the protein responsible for the repairing of oxidative DNA damage [131]. studies have shown that Oxidative stress causes a decline in the ability of DNA to repair oxidative damage, which results in a shortening of telomeres during aging [132]. Increased oxidative stress augments the expression of phosphorylated cyclin-dependent kinase inhibitor p16 (INK4a). Increased INK4a expression results in shortening the telomere length and aging in endothelial progenitor cells (EPCs) [133]. In-

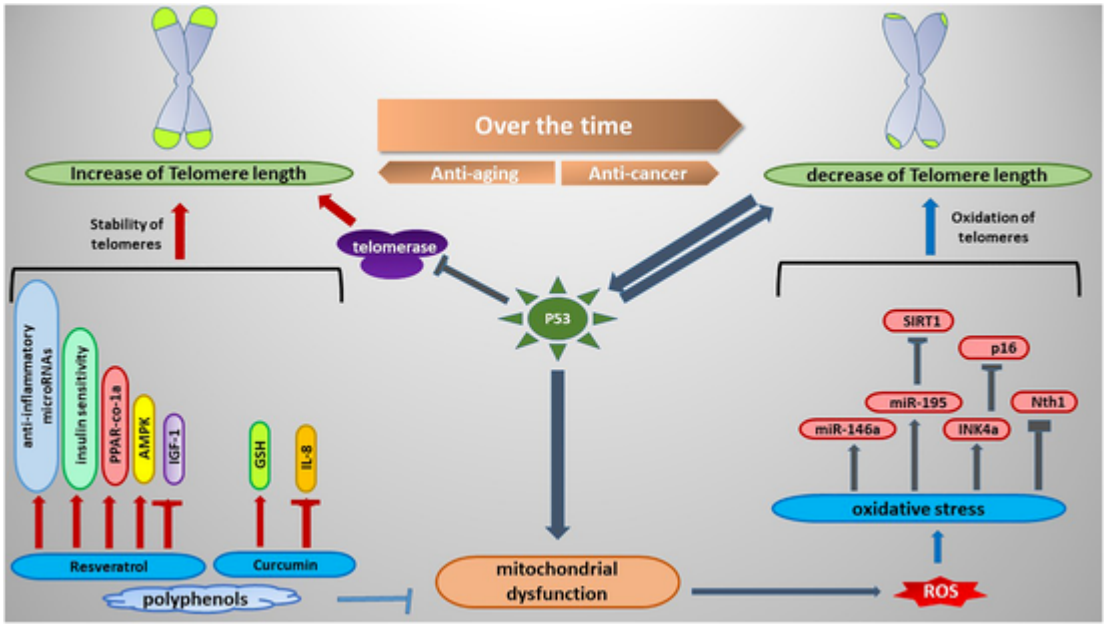

Fig. 3. Some of the molecular mechanisms of oxidative stress that lead to telomere shortening versus some of the molecular mechanisms of polyphenols that lead to telomere length.

creased oxidative stress may enhance the expression of miR-195 which inhibits SIRT1that leads to senescence-related to the shortening of telomeres [134]. Also, increased oxidative stress upregulates the expression of miR-146a which is one of the factors of human umbilical vein endothelial cells (HUVECs) aging due to telomere shortening [135–137] (Fig. 3).

The antioxidant effects of diet on telomere function indicate that diet is an important factor in determining telomere length status. A study of the Mediterranean diet rich in monounsaturated fatty acids, such as in the olive oil, showed that leukocyte telomere length is significantly increased in these subjects [138]. Another study showed that increasing the levels of beta-carotene and alpha-tocopherol in healthy Japanese adult's diet protects telomere length in buccal mucosal cells [139]. Also, It was suggested that a high intake of carotenoid-rich foods might play a role in protecting telomeres against oxidative damage [140].

Nowadays, researchers are trying to increase telomerase activity and preserving telomere length and prolonging life by using antioxidant supplements such as polyphenols [101]. Polyphenols are a class of naturally-occurring phytochemicals that many of the biological actions of these have been related to their antioxidant properties. Polyphenols have more anti-aging properties than other antioxidant substances due to their large numbers of hydroxyl (–OH) groups. Resveratrol, curcumin, catechin, and quercetin belong to the polyphenol group [63].

The polyphenols available in Grape are Resveratrol type. Besides grapes, this type of polyphenol is derived from various plants such as berries and peanuts. The anti-aging effects of this polyphenol have been demonstrated in vitro and in vivo [141,142]. Resveratrol augmented insulin sensitivity, AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor-c coactivator 1a (PPAR-co-1a) activity and anti-inflammatory microRNAs. Also, it diminished the expression of insulin-like growth factor-1 (IGF-1) (Fig. 3) [143,144].

Proanthocyanidins and procyanidins are polyphenols found in grape seed extract (GSE). These polyphenols are powerful free radical scavengers, possess anti-inflammatory properties, reduce apoptosis, prevent hydrogen peroxide (H2O2) induced chromosomal damage in human lymphoblastic cells. Their free radical scavenging capacity is 20 times more effective than vitamin E and 50 times more effective than vitamin C [145].

Curcumin (CUR) is one of the best anti-aging supplements. A yellow phenolic compound found in Indian curry spice turmeric acts as an antioxidant by increasing glutathione (GSH) levels and thereby counteracting the harmful effects of free radicals. It also has anti-inflammatory effects, possibly by inhibiting the release of IL-8 [146] (Fig. 3).

Tea is rich in polyphenols, carotenoids, tocopherols, ascorbic acid, minerals, and certain phytochemicals. A cross-sectional study of Chinese men and women found that elderly Chinese men had a positive association with telomere length. These compounds work in various ways, including scavenging harmful reactive nitrogen and oxygen species, acting as metal chelators, and inhibiting lipoxygenase, cyclooxygenase, and xanthine oxidase enzymes [147,148]. Another dietary flavonoid polyphenol that prevents aging is Quercetins. This polyphenol increases the cellular proliferation and viability of human HFL-1 by further activating proteasomes and antioxidant properties [149,150].

Therefore studies and evidence propose that polyphenols, with their antioxidant and anti-inflammatory properties, can affect telomere length and prevent shortening as far as possible and thus have potent anti-aging properties (Fig. 4).

7. Conclusion

Aging is an unavoidable process that affects the whole population and resulting in the development of diseases and eventually leads to death. Various molecular mechanisms such as genetic damages, which accumulation throughout the life, epigenetic alterations, metabolic pathways, for instance, insulin-like growth factor (IGF-1), mTOR, and PI3K-AKT signaling pathways, and also proteins and hormones hemostasis disturbances are involved in the occurrence of aging. One of the most famous of these is telomeres shortening, which is a marker of aging. Dietary patterns such as antioxidant consumption may be beneficial for telomere length maintenance and delay progressive aging. One group of these antioxidant compounds are polyphenols found in a variety of fruits (grapes, apples, pears, cherries, berries), tea, coffee, red wine, cereals, dry beans, and chocolate. Evidence suggests that oxidative stress and the free radicals produced by it play an essential role in telomere shortening through decreasing the activity of the telomerase enzyme. Polyphenols can prevent this occurrence by inducing the overexpression of antioxidant enzymes such as superoxide dismutase and

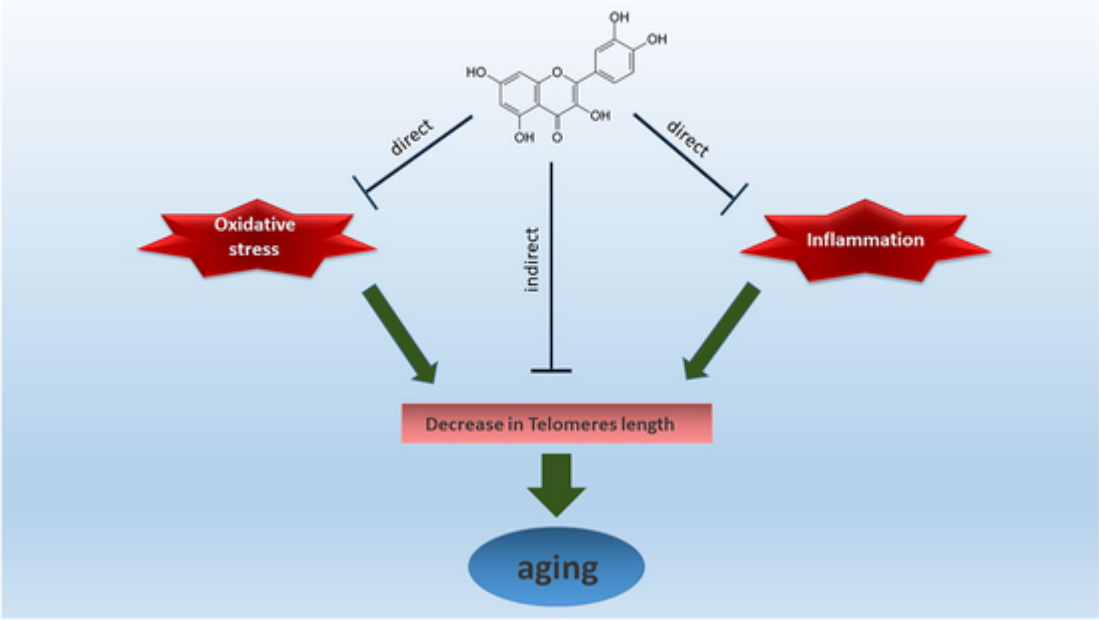

Fig. 4. Polyphenols prevent telomeres shortening with their anti-oxidant and anti-inflammatory properties and as a result play direct and indirect anti-aging roles.

catalase. Overall, rising intake of foods containing polyphenols can re duce age-related disease prevalence and Increases the life-span.

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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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