Pharmacological Treatment for Aging: Are We There?

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Abbreviations

5hmC	5-hydroxymethylcytosine
AA	Ascorbic acid
AD	Alzheimer disease
AMD:	Age-related macular degeneration
AMPK	5′ adenosine monophosphate-activated protein kinase
ATG-13	Autophagy-related gen 13
CD36	Cluster of differentiation 36
COX-2	Cyclooxygenase-2
CR	Calorie restriction
CRM	Calorie restriction mimetic
DNA	Deoxyribonucleic acid (DNA)
Elk-1	ETS Like-1 protein Elk-1 (Elk-1)
GSH	Glutathione
H3K27m3	Histone H3 trimethylation at amino acid position 27
HDCA	Histone deacetylase
IL-1α	Interleukin 1 alpha
Jmjd3	Jumonji domain containing-3
LMWA	Low molecular weight antioxidants
MAPK	Mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
mTORC1	mechanistic target of rapamycin complex 1
NAD	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen

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NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Nrf2/ARE	Nuclear factor erythroid 2 (NFE2)-related factor 2/ antioxidant responsive element
PD	Parkinson's disease
Raf1-MEK-MAPK	Raf-1- mitogen-induced extracellular kinase- mitogen-activated protein kinase
RONS	Reactive Oxygen and Nitrogen Species
ROS	Reactive species of oxygen
SASP	Senescence-associated secretory phenotype
TET	Ten-eleven translocation methylcytosine dioxygenase
ULK	Unc-51 like autophagy activating kinase
UQ	Ubiquinone
μM	Micromolar

Introduction

Human aging is known as a decline in the homeostatic reserve, leading to an accumulation of damage and therefore to the loss of several physiological functions, inducing an increase in the probabilities of death [1]. In addition, it is well known that this process has a strong correlation with the development of several age-related changes affecting appearance (like wrinkled skin and grey hair) and the organ functions, such as decreased kidney filtration rate and decreased muscular strength. On the other hand, the average lifespan has increased approximately by 3 months per year in both males and females since 1840, probably by the improvements in public health, education, and medicine. However, this increase in life expectancy is not accompanied by the same increase in healthspan [1], since aging is the leading risk factor for chronic pathologies and prevalence of age-related diseases, including, diabetes, arthritis, cancer, neurodegenerative diseases, among others.

On the other side, since the times of alchemy, humans have tried to expand lifespan through several methods with no or very few successes. However, until very recently, our knowledge of the main biological mechanisms involved in aging (refer to Chap. 1) have increased, and this has led to the development of several compounds focused on the regulation and manipulation of such. In this chapter, we focus on the main studies involved in the pharmacological test of both natural and synthetic compounds, due to their increasing use within the pharmacological research.

Antioxidant Compounds

The oxidative stress theory of aging proposes that age-associated losses are due to the accumulation of oxidative damage to macromolecules such as lipids, DNA, and proteins by reactive oxygen and nitrogen species (RONS) [2]. An increase in

RONS levels generates damage and cellular senescence [2]. Moreover, senescent cells acquire an irreversible senescence-associated secretory phenotype (SASP), which promotes the secretion of soluble factors, such as interleukins and chemokines, growth factors, degradative enzymes, such as matrix metalloproteases, and insoluble proteins/extracellular matrix components [2]. Most of these SASP components are highly related to the regulation of mTOR, the production of IL-1α, an increase in NF-κB activity, epithelial-mesenchymal transition, and metastatic tumor progression, among others. Oxidative stress is also involved in chronic kidney malfunction, neurodegenerative diseases, and cancer [2]. In this context, research has been focused on the development of agents that could be useful for the treatment of the redox state and nutrient-rich antioxidants that mediate oxidative stress [3].

Antioxidants are essential for the antioxidative defense mechanisms of the body; some of them are small molecules (<900 Da) that regulate the physiological processes of the body [4]. Among them are minerals, vitamins, carotenoids, glutathione, and polyphenols [5]. These can be classified into molecules that cannot be synthesized by humans, such as vitamin C and vitamin E [4], and those that can be synthesized, such as glutathione, lipoic acid, uric acid, taurine, melatonin, and coenzyme Q [6].

Glutathione

Glutathione (GSH) can be synthesized in the body from amino acids such as L-glutamic acid, L-cysteine, and glycine [7]. Interestingly, homeostasis of intracellular GSH is regulated by de novo synthesis [4]. Other properties of GSH are the metabolism of hormones, such as estrogens, leukotrienes, and prostaglandins, and signal transduction for transcription [8]. Alteration of GSH concentration is linked to dysregulation of cell proliferation, transcription of detoxification enzymes, and apoptosis [4].

Alteration in GSH-peroxidase and -reductase activity is found in diabetes [4]. In the brain, disruption in GSH homeostasis may induce oxidative stress and lead to neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease (AD), and dementia [4]. Studies show that a reduction in the levels of GSH is associated with AD [9]and cardiovascular diseases [10]. On the other hand, in PD exists an association with the depletion of GSH levels and an increase of ROS within the midbrain [11].

Flavonoids

Flavonoids are the most studied class of polyphenols; there is information available on about 6000 flavonoids, isolated from pigments, fruits, and medicinal plants [12]. Several properties have been associated with these compounds, such as antioxidative, antimutagenic, anti-inflammatory, and anticarcinogenic [13]. Particularly, several reports show the antioxidant effects of flavonoids in oxidative stress induced by age-related diseases [4].

In older women, it was reported that high total flavonoids intake reduced the risk of cancer mortality compared to low total flavonoids consumption [14]. Also, a decrease in breast cancer risk among postmenopausal women was found to be associated with flavonoids intake [15]. Other reports showed that two flavonoid subclasses, namely procyanidins and isoflavones, exert preventive effects toward the risk of the development of colorectal cancer [4]. In this context, studies demonstrated that consuming a flavonoid-rich diet is associated with a lower risk of cardiovascular diseases since flavonoids can prevent cardiovascular diseases by their anti-inflammatory, antioxidant mechanisms and by increasing the high-density lipoprotein level [4]. Additionally, in diabetes, flavonoids from green tea and epicatechin induce the activation of the insulin receptor.

Flavonoids from cocoa, green tea, and citrus fruit exert beneficial effects on the brain [4]. Evidence suggests that flavonoids protect against neural injuries and degeneration in pathologies like AD and dementia. Flavonoids have also been reported to downregulate the development of AD-like pathophysiology and related neurodegenerative disorders by disrupting amyloid β protein production, activating α-secretase, and inhibiting β-secretase [16]. Together, this evidence showed that flavonoids have the potential to block the initiation and progression of age-related diseases. Thus, a high intake of flavonoids should be included in the diet of the elderly via supplementation or flavonoid-rich food.

Carotenoids

Carotenoids are produced in the plastids of plants, algae, bacteria, and fungi [4]. There are approximately 600 carotenoids that have been discovered [17]. Two classes comprise the carotenoids: carotenes and xanthophylls [18]. They not only exert antioxidant properties but facilitate the modulation of the cell cycle, apoptosis, cell differentiation, and enhancement of the immune system and promote growth factors and adhesion molecules [4].

Carotenoids have a protective role in age-related macular degeneration (AMD), a leading cause of blindness in older adults. In the processes linked to AMD, it is described as the oxidative stress within the retina, besides the ROS generation [4]. However, it was found that individuals who consume a carotenoid-rich diet have a relatively low risk of age-related macular degeneration, indicating the positive effects of these molecules [19].

Other studies demonstrate that lutein may decrease the risk of cardiovascular diseases, coronary artery disease, and cancer [4]. It also inhibits breast cancer via modulation of NrF2/ARE and NF-κB pathways [20]. Another common carotenoid, lycopene, widely accepted as a potent antioxidant, reduces the risk of certain types of cancers, such as of the lung, prostate, and colon [4]. Lycopene suppresses the progression of carcinogenesis via its anti-inflammatory actions [21]. Interestingly, in a follow-up study conducted from 1986 to 2010 involving 49,898 males revealed that higher lycopene intake could prevent prostate cancer [22].

Studies in human and animal models suggested that carotenoids could reduce the risk of osteoporosis [23]. β-carotene significantly inhibited the viability of bone

marrow–derived macrophages and decreased the NF-kB pathway [4]. A meta-analysis involving 140,265 participants and 4324 cases suggested that high dietary intake of total carotenoids reduced hip fracture risk by 28% [24] and bone density and fracture risk were inversely correlated with dietary intake of carotenoids [25].

Studies showed that high plasma levels of lutein reduced the risk of neural disorders [4]. Interestingly, a high level of lutein, zeaxanthin, and lycopene in serum has been associated with a lower risk of AD mortality [4].

Dietary Minerals

The beneficial effect of mineral on aging is worth the attention; some minerals such as copper, magnesium, zinc, and selenium possess antioxidant properties. However, an overdose of mineral intake is not recommended and may cause a detrimental impact on health.

Zinc, an important mineral, that can be found in the retina and is implicated in the antioxidant defense system of the eye [26]. A study with 369 participants revealed that a low intake of zinc was associated with AMD [27]; additionally, a follow-up study for 6 years including 3640 participants revealed a significant role of zinc in AMD [28]. Similarly, a meta-analysis of 23,099 individuals demonstrated that dietary zinc blocks the progression of AMD and delays its progression [29].

Reports show, zinc supplementation may suppress oxidative stress induced by type 2 diabetes via insulin production and secretion processes [30]. Interestingly, zinc facilitates phosphorylation of the insulin receptor by allowing the transportation of more glucose into the cells. In this context, different studies showed that detection of thiobarbituric acid reactive substances in plasma was decreased in patients with type 2 diabetes treated with nutrimental supplements with zinc [30]. Evidence shows that zinc improves insulin sensitivity and reduces chronic hyperglycemia in type 2 diabetes [31]. Zinc suppresses the proliferation of cancerous cells by several mechanisms such as the inhibition of the mitochondrial terminal oxidation, electron transport and mitochondrial respiration, and the stimulation of the apoptogenic pathway [4]. Data from epidemiologic studies found that dietary zinc intake may reduce the risk of cancer [32]. In prostate cancer cells, zinc is accumulated in the expression of the zinc uptake transporter, ZIP1 [33]. The accumulated zinc exerts its antiproliferative activity toward the prostate cancer cells via activation of MAPK's [4]. In colorectal cancer, zinc was found to activate Raf-1-MEK-MAPK kinases, followed by the activation of Elk-1-dependent trans-reporter gene expression [4].

Ascorbic Acid (Vitamin C)

Ascorbic acid or vitamin C (AA) is a cofactor for many enzyme-catalyzed reactions, such as maintaining connective and vascular tissue's integrity, enhancing the collagen biosynthesis and iron absorption, modulating the leukocyte and hematopoiesis functioning, neuroprotection, and hydroxylation of lysine and proline [4].

Data from population-based studies show a correlation between aging and reducing ascorbate levels in tissues [4]. AA level reduces for nearly 50% in leukocytes in individuals at the age of 85 and above compared to those at the age of 60 [34]. Despite the limited available evidence on ascorbate level in human brains, a previous study has reported that ascorbate level in the cerebral cortex declines for nearly 77% of individuals at age 80 and older compared to those at age 50 and younger [35]. A study showed that ascorbate shortage contributes to the dysregulation of 5hmC, which subsequently contributes to age-related neurodegenerative diseases [36]. Research evidence has demonstrated the potential protective function of ascorbate in neurodegenerative diseases [4]. Ascorbate supplementation markedly improves the differentiation of midbrain-derived neural stem cells against dopaminergic neurons, which is associated with TET-mediated 5hmC generation and Jmjd3-catalyzed loss of H3K27m3 [37]. In this regard, these findings imply that ascorbate plays a critical role in dopaminergic neuron differentiation [4]. Studies show, a high concentration of AA induces cytotoxicity against cancer cells in vitro and can delay tumor growth in xenograft models [4]. Notably, some research has emerged to suggest that AA improved endothelial function in diabetic patients [38].

Vitamin E

Vitamin E usually, found in food, includes four tocopherols and four tocotrienols. Among all isoforms of vitamin E, γ-tocopherol is the primary form of vitamin E in the diet and exerts potent antioxidant properties [39].

An emerging role for tocopherols and tocotrienols in response to neuroinflammation has been demonstrated, and positive effects on oxidative damage and AD pathology have been proposed. The proposed aspects of the neuroinflammatory activity of this vitamin include the regulation of AD-associated enzymes, such as COX-2, 5-lipoxygenase, and NADPH oxidase [4]. Research evidence indicates that tocopherols and tocotrienols benefit in the stimulation of phosphoprotein phosphatase 2A, a phosphatase that plays a crucial role in tau homeostasis, which is lowered in human AD brains [40]. Moreover, data from clinical evidence showed that tocopherol and tocotrienol supplementation in AD patients reduces lipid peroxidation compared with the control [41].

Data from a cross-sectional study showed a positive relationship between bone mineral density and α-tocopherol level in the elderly Chinese population [42]. A beneficial effect of tocopherol and tocotrienol supplementation has also been documented on the incidence of cardiovascular disease. On the other side, the decrease of CD36 scavenger receptor expression indicates the role of tocopherols and tocotrienols in the reduction of foam cell formation and atherosclerosis [43]. Another report showed that tocopherols and tocotrienols reduced pain-debilitating symptoms elicited by painful inflammation. The reduction of cytokine production has also been demonstrated in humans with arthritis [44]. Overall, tocopherols and tocotrienols might be promising tools for alleviating oxidative stress and preventing age-related diseases.

Ubiquinone

Ubiquinone (UQ) or coenzyme Q10 is synthesized within the body cells or can be obtained from the diet [45]. Studies suggest, a reduction in the levels of UQ during aging may be involved in the predominant factors to develop age-related diseases [46]. Data from randomized controlled clinical trials demonstrated that supplementation with UQ induces an improvement in vascular dysfunction and decreases the glycemic response [47].

Another study reported that UQ enhances nerve conduction parameters of diabetic polyneuropathy and ameliorates oxidative stress without significant undesirable effects [4]. As well as evidence further supported that UQ increases insulin sensitivity and improves β cell function in diabetic patients [48].

In the case of neurodegenerative diseases, UQ plays a central role in the cellular dysfunction of PD since levels of UQ were relatively low in patients [4]. On the other hand, the treatment with UQ reduced the cellular pathophysiological alterations related to mitochondrial dysfunction in PD patients. These results show that a high concentration UQ administration may downregulate the functional decline experienced during the early stage of patients [4].

Calorie Restriction and Its Effect on Aging

The reduction of calories by 10–30% compared to a typical diet prolongs the longevity of different species; moreover, it is known that several alchemists had long periods of fasting as a common practice [49]. Studies suggest that caloric restriction (CR) may decrease the levels of insulin and blood pressure in humans [50]. These findings support the hypothesis that CR could delay the effects of age [51].Thus, several compounds have calorie restriction mimetic (CRM) activities and have the ability to mimic the anti-aging effects of CR.

Resveratrol

It is a polyphenol compound isolated from the skins of red grapes. Of all the most-studied CRM's, resveratrol ranks first. Resveratrol was published as CRM through the selection of small molecular libraries for compounds that activate sirtuins and extend the shelf life of different organisms (yeast, worms, flies, fish, and mice) [52, 53]. Resveratrol triggers the expression of antioxidant enzymes; additionally, it stimulates the activity of SIRT1 and AMPK and metabolic regulators of tissues [54]. The results of the research showed that it could mimic the benefits associated with caloric restriction. In this context, resveratrol was administered to 38 obese subjects and showed an increase in mitochondrial activity and fat oxidation [54]; on the other side, in another clinical study with 17 volunteers with type 2 diabetes, a decrease in systolic blood pressure and intrahepatic lipid content were observed after treatment [55]. Although the effect of extending the longevity of resveratrol

has not been fully verified in humans, and clinical results of studies are quite promising, several works have shown contrasting effects of resveratrol due to the different conditions that are managed, such as the number of participants, their age, sex, health status, lifestyle, dose, environment (with or without food), and type of administration (capsule, tablet, powder, gel capsules, among others). So considering these aspects in future studies on the effects of resveratrol could help to study in greater depth the mechanisms of action of this compound [56].

Rapamycin

Rapamycin is a macrolide isolated from *Streptomyces hygroscopicus*, a bacteria from Pascua Island (Rapa Nui). It has functions as an antibiotic, an immune suppressant drug, and it is also proposed as a CRM. After the first studies, it was found that rapamycin could induce the extension of the replicative life of yeast through the inhibition of TOR signaling [57]. This compound could extend the lifetime useful in 20-month-old mice in correlation with TOR activity [58]. These studies were the basis of the research to determine the function of rapamycin as a CRM, due to its modulating properties over proteostasis. In addition, studies suggest that rapamycin can be combined with other compounds (metformin, losartan, statins, propranolol, and aspirin among others) to potentiate their anti-aging activity [59].

Metformin

Metformin has gained importance in gerontology since it has several functions, such as being a medication used for the treatment of type 2 diabetes by increasing insulin sensitivity and AMPK activity. Their CRM activity was assessed since metformin treatment enhances insulin sensitivity, glycolysis, and suppresses gluconeogenesis. Recently, it was proposed that metformin might increase the longevity of frailty patients [60]. In this context, several studies confirmed the longevity effect of metformin on worms, mice, flies, and rats [61]. Interestingly, in diabetic and cardiovascular disease patients treated with metformin, rates of survival have increased [62, 63]. Moreover, treatment with metformin among patients with diabetes reduces the risk of dementia [64].

Inductors of Autophagy and its Impact on Aging

Autophagy has a role in homeostasis, which plays an essential role in the maintenance of cellular physiology and the prevention of cellular damage. Among the inducers of autophagy have been described the already-mentioned rapamycin, resveratrol, and polyamines; however, only polyamines have demonstrated results in clinical research in humans [65]. It is known that these compounds can induce the canonical autophagy pathway, which includes inactivation of the mammalian

objective of the rapamycin complex 1 (mTORC1), allowing phosphorylation and activation of the Unc-51 complex (Ulk1/2), where the cascade of the other members of the complex is subsequently activated, ULK as FIP200 and ATG13 [65].

Polyamines

Spermidine is a polyamine capable of inducing the macroautophagy of cells. It induces autophagy by inhibiting acetyltransferases, such as EP300 [66], one of the essential negative regulators of autophagy. Studies show that it has a potential for activity equivalent to that of rapamycin as an autophagy activator [67]. Spermidine prolongs the lifespan and duration of the health of various organisms, such as yeasts, nematodes, flies, and mice. In humans, spermidine levels reduced during aging, suggesting the association of the reduction of these levels with the deterioration associated with age. Epidemiological evidence supports that foods rich in spermidine counteract cardiovascular diseases and cancer [68].

Senolytic Compounds

During aging, these senescence cells accumulate in many tissues and pathological sites in multiple chronic diseases. Senolytic compounds are agents that selectively induce death in senescent cells [69]. Studies showed that the treatment of senescent cells with genetic or pharmacological methods delays, prevents, or improves multiple phenotypes related to age [70]. So, it is important to expand the use of these compounds in clinical studies to be able to include the effects of testing on multiple morbidities. If the senolytics drugs or other interventions directed to the processes of fundamental aging happen to be effective and safe in the clinical tests, these could transform geriatric medicine, allowing the prevention or the treatment of multiple diseases and functional deficits [71].

Several compounds showed to be senolytic compounds: *Curcumin* (a constituent of the rhizome of turmeric, eliminated the senescent cells of the intervertebral disc obtained from patients, as well as reduced the SASP), *Quercetin* (a flavonoid, found in dietary plants; this compound was found in combination with the anti-cancer drug dasatinib and had efficacy as senolytic in several types of senescent cells), *Rapamycin* (a macrolide which inhibits mTOR, is shown to improve health, and inhibits cellular senescence in multiple cell types; it inhibits cellular senescence in vitro and increases longevity in several species), *Berberine* (an isoquinoline alkaloid that has the ability to modulate senescent cells so it can potentially be used as a senolytic drug), *Piperlongumine* (an alkaloid isolated from long pepper, has the ability to preferentially induce cell death in senescent WI-38 fibroblasts generated by both radiation and replication and induced by oncogenes), *Fisetin* (a flavonoid present in fruits and vegetables that induces apoptosis in senescent HUVEC cells), and *Phloretin* (a flavonoid that at a concentration of 50 μM reduces the viability of senescent lymphoma cells [71]).

Although these are preliminary results, the impact that the senolytics will have on human health and illnesses is still unknown. It is interesting to determine the phenomenon that would happen if the senescent cells were eliminated from organisms and if aging and dysfunction would be delayed or pathological processes would be triggered [72]. Studies in mice have found that senotherapy can prevent, stop, and reverse different age-related diseases [73]. Recently, in the first pilot study performed in humans (14 patients), senolytics drugs (dasatinib and quercetin) were used to treat Idiopathic Pulmonary Fibrosis; it was proved to be encouraging, since results showed that targeting senescent cells can alleviate the functional consequences of diseases in humans [74]. Later, a second preliminary study from a clinical trial of dasatinib plus quercetin in individuals with diabetic kidney disease showed important findings, which were verified not only in analysis of blood but also in changes in skin and fat tissue senescent cell abundance, with a decrease in circulating SASP factors [75].

Activators of Telomerase

Telomerase is an enzyme with reverse transcriptase activity whose function is to replicate DNA at the ends of eukaryotic chromosomes, thus lengthening telomeres. However, telomerase is repressed after birth, resulting in a shortening of the telomere after each cell division. Evidence shows that a reduction in telomerase activity causes cells to bypass senescence [76].

The overexpression of telomerase in mice shows that it was sufficient to delay different pathologies associated with age as cognitive deterioration [77]. The activators of telomerase are important for the development of anti-aging compounds. The most studied activator low-power telomerase TA-65 (isolated from *Astragalus membranaceus*) was shown to induce a slight increase in telomere length in humans [78] as well as improve several age-related parameters.

Drugs with Effects over Epigenetics and Aging

The epigenetic drugs have shown quite exciting results in the aging research field because they are capable of modulating the enzymes involved in gene-environmental mechanisms associated with age-related diseases. Drugs designed to modulate epigenetic targets, such as HDAC inhibitors, have been used in clinical trials. It is known that the therapeutic application of HDAC inhibitors resulted in the affectation of the transcription of several genes and processes, such as the suppression of tumors due to transcriptional reactivation of silent tumor suppressor genes and the transcriptional repression of proto-oncogenes [79]. Numerous studies have identified HDAC inhibitors as candidate drugs for the treatment of neurodegenerative disorders. Therefore, the development of specific drugs aimed at HDAC activity could be an anti-aging strategy with encouraging results.

On the other side, in recent years the therapeutic modulators of NAD-dependent class III histone deacetylases, so-called sirtuins, have caught attention for aging research since they seem to play a key role during cell response to a variety of stresses (oxidative or genotoxic) and are involved in senescence [80]. Evidence suggests that the activation or inhibition of sirtuins [81] may be useful to prevent or treat age-related diseases, where they showed protection against neurodegenerative diseases [82]. For instance, selective inhibitors of SIRT2 and AGK-2 has been reported to have protective effects against PD and in the treatment of AD [82]. Additionally, the inhibition of Sirt1 showed to sensitize cells for DNA-damaging cancer therapeutics and decrease tumor growth; some of them are already in clinical trials.

Conclusions

As seen in this chapter, several compounds have anti-aging functions, such as antioxidants, CRM, autophagy inducers, senolytic compounds, among others, and may have the ability to possess anti-aging activity because they participate in the regulation of both the route and factors involved in aging. Although most of the results obtained from different investigations are still preliminary, it is worth mentioning that in recent years, clinical trials have begun in humans, with promising results; so more in-depth research should be carried out of these compounds, since the understanding and generation of molecular mechanisms generated using all these molecules could help us to develop new drugs for the treatment and prevention of chronic diseases associated with age.

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