Chapter 22
Gerosuppressive and Senolytic Nutrients

Jan O. Nehlin

Abstract The aging process is intimately regulated by the contribution of interactions between genetic, epigenetic and environmental factors. Every individual is distinguished by a specific personal lifestyle, since conception, that influences the state of health, either leading to the preservation of a good state of health or accelerated aging trajectories that could hasten the occurrence of disease. The intake of specific nutritional factors, investigated in large epidemiological studies, have long been considered associated with specific health outcomes and prevention of health problems. As a result of the aging process, the occurrence of senescent cells within the body can cause damage to organs and tissues leading to many age-associated pathologies. The advent of the nutritional geroscience field is contributing to reveal how a diverse number of phytochemicals can help to reduce the rate of cell proliferation, enhance cellular function, eradicate senescent cells, or suppress, at varying degrees, their abnormal secretomes, mitigating the extent of damage posed by them in the body. A summary of senotherapeutic biomolecules acting as senolytics and gerosuppressors will be here presented, to strengthen our knowledge that natural compounds present in the diet, when given at the right time, at the right dose and in combination, could extend the duration of health span and the overall lifespan.

Keywords Health · Disease · Aging · Senescence · Gerosuppressor · Senolytic

22.1 Introduction

Since conception, humans are exposed to a nutritional environment that will shape their future health trajectories, during all their lifetimes. The interplay between nutritional lifestyle, parental epigenetic factors, and inherited gene variants will determine how well the body will function and cope with all the stresses that will be confronted with time.

J. O. Nehlin (✉)
Department of Clinical Research, Copenhagen University Hospital Amager and Hvidovre-Copenhagen, Kettegård Alle 30, 2650 Hvidovre, Denmark
e-mail: jan.nehlin@regionh.dk

S. I. S. Rattan and G. Kaur (eds.), *Nutrition, Food and Diet in Ageing and Longevity*, Healthy Ageing and Longevity 14, https://doi.org/10.1007/978-3-030-83017-5_22

Traditional medicine, through thousands of years of experience, has contributed to unravel the identities of natural products that could have a role in preserving health, mitigating symptoms of disease, accelerated healing, and general well-being (Mukherjee et al. 2017; Wang et al. 2018). The chemical identification of the active ingredients with both beneficial and detrimental roles has been ongoing for decades.

The health benefits of Mediterranean and Asian diets have been confirmed in many clinical trials and epidemiological surveys. These diets are characterized by several features, including low meat consumption, fish consumption, the intake of oils instead of fats as lipid sources, moderate amounts of red wine, and significant amounts of fresh fruit and vegetables. Polyphenols have been shown to have multiple health effects as demonstrated by several relevant population studies and clinical trials (Leri et al. 2020; Cannataro et al. 2021; Shen et al. 2017; Gensous et al. 2020; Quach et al. 2017). The cellular mechanisms by which polyphenols exert their function has been recently reviewed (Russo et al. 2020; Mansoori et al. 2021; Jantan et al. 2021) as well as the role of polyphenols against aging and cancer (Bian et al. 2020; Russo et al. 2020).

The role of the microbiota needs to be highlighted in relation to healthy aging, because it is intimately associated with the specific intake of nutrients, and long-term health consequences (Fragkou et al. 2021, Tavella et al. 2021), as well as parameters such as eating time (Taetzsch et al. 2021).

22.2 General Considerations

Senescent cells arise in the body during development, stress, disease and aging (Childs et al. 2017). Several mechanisms can lead to senescence including replicative senescence (RS), stress-induced senescence (SIPS), oncogene-induced senescence (OIS), mitochondrial dysfunction-associated senescence (MiDAS), and many more (Di Micco et al. 2021; Calcinotto et al. 2019).

The immune system targets senescent cells that harbor damage that could pose a potential risk if allowed to bypass the senescent state (Prata et al. 2018, Kale et al. 2020). However, with time, immune function gradually decays giving rise to immunosenescence. The immune cells responsible for targeting and eliminating senescent cells become reduced in number and function, thereby allowing senescent cells to accumulate in the body (Rodrigues et al. 2021, Prata et al. 2018, Kale et al. 2020). The accumulation of senescent cells results in the characteristic low-grade chronic inflammation that is associated with age, which causes organ dysfunction (Childs et al. 2017; Furman et al. 2019).

Aging is a universal living condition that is accompanied by an increased risk of age-associated diseases, all of which are gathered under the concept of geriatric syndrome. The World Health Organization (WHO) has categorized senescence as a significant risk factor behind the origin of older age diseases (Code MG2A: Old age; International Classification of Diseases (ICD) 11th (June 2018). Senolytics (see

Sects. 22.3 and 22.4) are considered an aid to prolong the state of disease-free lifetime in people (Khaltourina et al. 2020).

22.3 Definitions and Classification of Senotherapeutics

Senotherapeutics or gerotherapeutics are compounds, medicines or protocols that exert senotherapy, an intervention targeting senescent cells, being considered an emerging strategy for the extension of health span, and prevention or treatment of age-associated diseases. At present, senotherapeutics can be classified in:

(1) Senolytics; (2) Gerosuppressors (SASP modulators or inhibitors); (3) Geroprotectors; (4) Epigenetic modifiers; (5) Gene therapeutics

The first four classes of senotherapeutics include nutritional components, whereas gene therapy strategies are mostly aimed at editing genes that might predispose to accelerated aging, less successful aging and even, enhance polymorphic variants to increase the length of health span, postpone the appearance of aging-associated diseases and extend lifespan.

The present work will consider the nutritional aspects involved in aging and focus on those compounds that exhibit senolytic and gerosuppressive functions. The nutritional geroscience field aims for the identification and characterization of nutritional compounds that have an effect on the function and/or viability of senescent cells, as well as health promoting activities that reduce or postpone the genesis of senescence. Some recent works have presented a list of senotherapeutics that are either in the discovery phase or are at different stages of clinical trials (Prasanna et al. 2021; Kirkland and Tchkonia 2020; Paez-Ribes et al. 2019; Morsli and Bellantuono 2021; Short et al. 2019).

22.4 Senolytics

Senolytics are defined as a new class of drugs that selectively kill senescent cells. They comprise small molecules that specifically induce cell death in senescent cells, targeting a number of targets including survival pathways and anti-apoptotic mechanisms (Zhu et al. 2015; Yosef et al. 2016). Several recent reviews have dealt with the topic of senolytic compounds (Kirkland and Tchkonia 2020; Martel et al. 2020; Robbins et al. 2021; Short et al. 2019).

Most studies on senolytics so far have focused on the effects of senescent cell eradicators in cell culture and mice studies. Such studies have rendered a great deal of knowledge as regards the specificity and extent of senolytic compounds on the alleviation of the senescent cell burden on specific tissues and their corresponding pathologies, including idiopathic pulmonary fibrosis (Justice et al. 2019), renal fibrosis post-acute kidney injury (Li et al. 2021), diabetic kidney disease (Hickson et al. 2019), eye age-macular degeneration (Lee et al. 2021), bone loss (Farr et al. 2017; Chandra

et al. 2020), cardiac ischemia–reperfusion injury (Dookun et al. 2020b), cardiovascular disease (Dookun et al. 2020a, Song et al. 2020), osteoarthritis (Dai et al. 2020; Jeon et al. 2017), diabetes (Palmer et al. 2021, Thompson et al. 2019), cognitive decline (Bussian et al. 2018), uterine fibrosis (Cavalcante et al. 2020), cancer (Picallos-Rabina et al. 2020), frailty (Xu et al. 2018), etc. The first documented study to report the elimination of senescent cells in vivo in humans by senolytics was the report by Justice et al., in idiopathic pulmonary disease (Justice et al. 2019).

Many ongoing pre-clinical and clinical trials (Kirkland and Tchkonia 2020; Prasanna et al. 2021) will provide unequivocal evidence of the role of senolytics in a variety of human aging-associated diseases (Childs et al. 2017).

Several phytochemicals belonging to the flavonoid family have been documented to exhibit potent senolytic activities (Yousefzadeh et al. 2018). A list of foods describing their flavonoid contents and amounts is available (Haytowitz et al. 2018). Early epidemiological studies already showed that the intake of foods containing flavonoids such as quercetin, kaempferol, myricetin, apigenin, and luteolin, was significantly inversely associated with mortality from coronary heart disease (Hertog et al. 1993).

Many senolytics can upregulate SIRT1 activity, a sirtuin that belongs to the family of class III histone deacetylases, whose enzymatic activity is dependent on NAD^+. SIRT1 is implicated in the cellular response to caloric restriction and lifespan extension (Iside et al. 2020). Several natural compounds that activate the Nrf2 (nuclear factor erythroid-derived 2-related factor 2) pathway, controlling the cellular response to stress caused by reactive oxygen species (ROS), have been found to be senolytic (Malavolta et al. 2018).

While senolytics seem to be very promising compounds, there are concerns as regards their possible side effects or disadvantages, if their administration exceeds specific concentrations, and duration, and whether the recipient suffers or not from an age-associated disease (Martin et al. 2021, Raffaele et al. 2021). For such reasons, the National Institute on Aging, USA, has called for standardization in the investigations and measures regarding senotherapeutic use, including reports on the balance between senolytic and cytotoxic effects, markers of specific senescent cell types linked to the specific interventions, interactions with coexisting diseases and their effects at various ages, especially in older people (Romashkan et al. 2021).

Senolytics can be classified as being of nutritional origin or pharmaceutical origin. Both classes will be addressed in this summary, with focus on senolytics from natural sources.

22.4.1 Nutritional Senolytics

Nutritional senolytics are compounds that originate from natural sources and exhibit senolytic activity. The most studied nutritional senolytics are presented, but the list is likely to grow further as more research will reveal whether known or novel polyphenols possess senolytic activities.

Below, a list of prominent, well-documented, nutritional senolytic compounds (in alphabetical order) aims to describe their origin, targets and possible uses in senotherapy.

22.4.1.1 Allicin

Allicin (diallyl thiosulfinate) is a volatile sulfur compound present in garlic (*Allium sativum*), a vegetable with multiple health effects (Borlinghaus et al. 2021). The health-promoting and disease-preventing effects of garlic on many human common diseases, such as cancer, cardiovascular and metabolic disorders, blood pressure, and diabetes, through its antioxidant, anti-inflammatory, and lipid-lowering properties, have been documented in vitro, in vivo, and clinical studies (Ansary et al. 2020). Allicin has antiproliferative, anticlonogenic, and senolytic effects. In addition, allicin decreased cell viability and induced apoptosis by loss of $\Delta\Psi m$, caspase-3, caspase-8, and caspase-9 activation, upregulation of NOXA, P21, and BAK, as well as downregulation of BCL-XL expression in breast cancer cell lines (Rosas-Gonzalez et al. 2020).

22.4.1.2 Curcumin and Curcumin Analogues

Curcumin is a yellow polyphenolic pigment from the turmeric (*Curcuma longa L.*) rhizome that has traditionally been used in culinary and food coloring, and as an ingredient in Ayurveda and Chinese medicine health promotion and disease prevention (Sharifi-Rad et al. 2020). Numerous studies suggest that curcumin has some health benefits in delaying aging and may be useful in preventing and treating age-related diseases (Cherif et al. 2019, Zia et al. 2021; Sharifi-Rad et al. 2020; Bielak-Zmijewska et al. 2019). Curcumin has been shown to have senolytic activity (Yousefzadeh et al. 2018). Among four commonly used curcumin analogs, EF24, HO-3867, 2-HBA and dimethoxycurcumin (DIMC), EF24 is the most potent and broad-spectrum senolytic agent. EF24 exerts selective lysis of senescent cells through the induction of apoptosis in a reactive oxygen species (ROS) production independent manner but associated with an increase in the proteasome degradation of the Bcl-2 anti-apoptotic protein family proteins known to play an important role in protecting senescent cells from apoptosis (Li et al. 2019).

22.4.1.3 Fisetin

Fisetin, with the chemical name 2-(3,4-Dihydroxyphenyl)-3,7-dihydroxy-4*H*-1-benzopyran-4-one, a flavonol, is a secondary metabolite of many plants, occurring in their green parts, fruits, as well as in barks and hardwood, that has anti-inflammatory, chemopreventive, chemotherapeutic and recently also senotherapeutic roles. Fisetin is present in strawberries, apples, persimmons, grapes, onions, kiwi, kale, nuts, smoke

tree (*Cotinus coggygria*), etc. (Grynkiewicz and Demchuk 2019; Mehta et al. 2018) and influences many cellular pathways (Kashyap et al. 2019). Fisetin is considered a senolytic because it was found to selectively induce apoptosis in senescent but not proliferating human umbilical vein endothelial cells. However, it was not shown to be a senolytic in a senescent human lung fibroblast strain, or primary human preadipocytes (Zhu et al. 2017). Fisetin was found to be the most potent senolytic in a panel of ten flavonoid polyphenols using senescent mouse and human cells. Moreover, when given to wild-type mice late in life, fisetin restored tissue homestasis, reduced age-related pathologies, and extended median and maximum lifespan (Yousefzadeh et al. 2018). Fisetin is one of the senolytics that has been shown to have toxic effects when administered in high dosis (200 μM) in rat, inducing mitochondrial pro-oxidant activity (Constantin et al. 2011). Fisetin has other side effects such as the promotion of hair growth by activation of telomerase reverse transcriptase (TERT) expression in skin hair follicle bulge stem cells (Kubo et al. 2020). A summary of the in vivo evidence for fisetin targeting multiple age-associated dysfunctions and pathologies in mammals has been presented (Morsli and Bellantuono 2021).

22.4.1.4 Luteolin

Luteolin, with the chemical name 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-chromenone, is a flavone, subclass of flavonoids, which is found in many vegetables, spices, fruits and medicinal herbs. It has many health benefits, and appears especially suited to alleviate the symptoms of glycolipid metabolism disorders such as insulin resistance, diabetes, and obesity (Wang et al. 2021). It was shown to have weak senolytic activity, in a comparative study with other flavonoids (see 4.1.3) (Yousefzadeh et al. 2018) but it has powerful anti-inflammatory actions in concert with IL-37 and IL-38 interleukins (Conti et al. 2021). Luteolin diminishes human neutrophil inflammatory responses by inhibiting Raf1-MEK-1-Erk, significantly inhibited superoxide anion generation, ROS production, and neutrophil extracellular trap (NET) formation in human neutrophils. The increase in elastase release, CD11b expression, and chemotaxis was also inhibited by luteolin (Yang et al. 2018). Apart from being anti-oxidative and anti-inflammatory, luteolin plays an important role in defending plants, for example against UV radiation, suggesting it could be useful in skin protection against UV-induced photoaging (Gendrisch et al. 2020).

22.4.1.5 Ortho-Vanillin

ortho-Vanillin (o-Vanillin; 2-hydroxy-3-methoxybenzaldehyde) is an organic solid present in the extracts and essential oils of many plants. o-Vanillin is an isomer of meta-Vanillin, a phenolic aldehyde.

Vanillin (4-hydroxy-3-methoxybenzaldehyde) that is a major component of the bean and pod of some plant species of the Vanilla genus, and is also synthesized on a

large scale for use as a flavoring agent in food, fragrance and pharmaceutical industries. Vanillin exhibits antioxidant, antimicrobial, analgesic, anti-carcinogenic, antimutagenic and anti-sickling biological effects (Marton et al. 2016). o-Vanillin cleared senescent intervertebral disc (IVD) cells and reduced the senescence-associated secretory phenotype (SASP) (see Sect. 22.5) associated with inflammation and back pain. It also increased metabolic activity, caspase 3/7 activity, and apoptosis in cells from degenerate IVDs, but not in cells from non-mildly-degenerate IVDs (Cherif et al. 2019). o-vanillin exerts its actions through increased pro-apoptotic pathways and reduction of expression of senescence-associated genes. (Cherif et al. 2020). The vanillin analogues o-vanillin and 2,4,6- trihydroxybenzaldehyde were also shown to be cytotoxic against cultured human melanoma A375 cells, and are therefore being evaluated as potential anticancer drugs (Marton et al. 2016).

22.4.1.6 Piperlongumine

Long pepper (*Piper longum L.*), commonly known as "Pippali", is a pepper plant found in India and southeast Asia, that contains a vast number of health promoting compounds. Piperine and piperlongumine are its two major piperidone alkaloids (Yadav et al. 2020). Piperlongumine (also called piplartine or piperlongumin) has many pharmacological activities and is commonly used in Ayurvedic medicine (Bezerra et al. 2013). Piperlongumine has been shown to exert senolytic activity (Wang et al. 2016) with at least 172 different senolytic targets. One of them is oxidation resistance 1 (OXR1), an important antioxidant protein that regulates the expression of a variety of antioxidant enzymes and provides senescent cells with high resistance to oxidative stress. Piperlongumine induced OXR1 degradation through the ubiquitin–proteasome system in a senescent cell-specific manner (Zhang et al. 2018). Among other relevant targets, piperlongumine can also bind to annexin A1 (ANXA1), an endogenous anti-inflammatory mediator with therapeutic potential in cancer (Henrique et al. 2020).

22.4.1.7 Quercetin

Quercetin is a polyphenolic flavonoid, chemically known as 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one, that is enriched in apples, berries, broccoli, cabbage, capers, cauliflower, cherries, citrus fruits, coriander, honey, nuts, red onions, tea, etc. (Batiha et al. 2020).

Quercetin was the first nutritional compound shown to have senolytic activity, and it was most effective against senescent human endothelial cells and mouse bone marrow mesenchymal stem cells. Quercetin was found to lack senolytic efficacy in senescent preadipocytes and mouse embryonic fibroblasts, but when combined with the anticancer drug Dasatinib, it was shown to be effective as senolytic in several types of senescent cells (Zhu et al. 2015).

In animal models, a senolytic cocktail of Dasatinib and quercetin (see also Sect. 22.4.2), which caused the elimination of senescent cells from adipose tissue, resulted in improved physical function and lifespan extension (Xu et al. 2018).

A clinical trial of Quercetin (Q) and Dasatinib (D) (a pharmaceutical senolytic; see Sect. 22.4.2) reduced the senescence burden in individuals with diabetic kidney disease (Hickson et al. 2019). Quercetin together with fisetin are considered as potentially useful adjuvants chemotherapeutic agents in the treatment of cancers, in view of their roles in modulating many cancer signalling pathways (Kashyap et al. 2019). The senolytic drug combination, D+Q, is known to reduce senescent cell abundance in aged mice, extending lifespan (Xu et al. 2018). D+Q senolytic treatment also has been shown to reduce intestinal senescence and inflammation while altering specific microbiota signatures (Saccon et al. 2021). A summary of the in vivo evidence of D+Q targeting multiple age-associated dysfunctions and pathologies in mammals, has been presented (Morsli and Bellantuono 2021).

22.4.1.8 Sulforaphane

The isothiocyanate sulforaphane (SF) is one of the most potent naturally occurring Phase 2 enzymes inducers derived from *Brassica* vegetables like broccoli, cabbage, brussel sprouts, etc. (Yuanfeng et al. 2021). Sulforaphane-induced cell cycle arrest, senescence by upregulation of cell cycle inhibitors p21 and p27, DNA hypomethylation and changes in microRNA profile in breast cancer cells (Lewinska et al. 2017). Another compound from cruciferous vegetables, Phenethyl isothiocyanate (PEITC) modulates the senescence effectors p16, p53, and p21, and induces increased staining of senescence-associated SA-β-Gal senescence biomarker (Malavolta et al. 2018).

22.4.1.9 Other Senolytic Compounds Based on Natural Products

Novel senolytic compounds were searched from natural products using chemoinformatic tools. Hinokitiol found in the roots of the Hinoki tree, preussomerin C from the *Lasiodiplodia theobromae* fungus, and tanshinone from *Salvia miltiorrhiza* Bunge roots, could be considered senolytic compound candidates since they share similarities in structure with senolytic leads such as tunicamycin, ginsenoside Rb1, ABT-737, rapamycin, navitoclax, timosaponin A-III, digoxin, roxithromycin, and azithromycin, and targets involved in senescence pathways with potential use in the treatment of age-related diseases (Barrera-Vazquez et al. 2021). An extract from the plant *Solidago virgaurea subsp. alpestris*, also known as goldenrod, is traditionally used as an anti-inflammatory herbal medicine, and was shown to exhibit weak senolytic activity (Lammermann et al. 2018).

Triptolide (TPL) is a diterpenoid extracted from the plant, *Tripterygium wilfordii Hook F*, which is a traditional Chinese medicinal herb. Bioactive TPL showed immunosuppressive, anti-fertility and anti-cystogenesis activities. TPL accelerated liver cancer cell line HepG2 cell senescence by regulating the AKT pathway. TPL

could also enhance cellular senescence and inhibit tumor growth by negatively regulating human telomerase reverse transcriptase (hTERT) signaling pathway (Li et al. 2017).

Senotherapeutics have also been identified in marine dietary algae such as (2R*, 3S*, 6R*, 7S*, 10R*, 13R*)-7,13-Dihydroxy-2,6-cyclo-1(9),14-xenicadiene-18,19-dial derived from *Dilophus fasciola*, Laurendecumenyne A from *Laurencia decumbens* and 4-Bromo-3-ethyl-9-[(2E)- 2-penten-4-yn-1-yl]-2,8-dioxabicyclo[5.2.1]decan-6-ol from *Laurencia sp.* to be potent inhibitors of multiple target senescent-cell anti-apoptotic pathway proteins (Salekeen et al. 2021).

22.4.2 Pharmaceutical Senolytics

Pharmaceutical senolytics are compounds that have been chemically synthesized and that, originally, were used as experimental cancer drugs. Cancer cells avoid apoptosis and can undergo tumorigenesis, in part by upregulation of pro-survival proteins of the Bcl-2 protein family (Bcl-2, Bcl-XL, Bcl-w, Mcl-1, and A1). Upon further investigation, some of the cancer drugs were found to target senescent cells in tumors, such as navitoclax (previously called ABT-263) that targets Bcl-2, Bcl-xl, and Bcl-w (Zhu et al. 2016; Prasanna et al. 2021). Combinations of pharmaceutical senolytics (e.g. Dasatinib) and nutritional senolytics (e.g. quercetin) have proven very effective in anti-senescent cell elimination (Saccon et al. 2021; Morsli and Bellantuono 2021). These findings have triggered further work to try to repurpose other existing pharmaceuticals to target aging pathways (Vaiserman et al. 2021).

Since pharmaceutical senolytics are drugs, that are not present in nutrients or foods, they will not be addressed specifically in this chapter.

22.4.3 Other Senolytic Strategies

The present work is focused exclusively on nutritional factors affecting senescent cells, however, many non-nutritional approaches are being considered as well, to influence and/or erradicate senescent cells. Examples include exercise (Chen et al. 2021b), fibrates (Nogueira-Recalde et al. 2019), hyperbaric oxygen therapy (Hachmo et al. 2020), chemically-based prodrugs such as a non-toxic derivative of the compound 5-Fluorouridine, a senescence-specific killing compound 1 (SSK1) derived from the drug gemcitabine targeting lysosomal beta-galactosidase (Cai et al. 2020), galactose-modified cytotoxic prodrugs such as Duocarmycin (Guerrero et al. 2020), cardiac glycosides targeting the Na^+/K^+ ATPase pump such as digoxin, in combination with senogenic compounds Gemcitabine or Doxorubicin (Triana-Martinez et al. 2019; Martin et al. 2020), inhibitors of the HSP90 chaperone family such as 17-Dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG) (Fuhrmann-Stroissnigg et al. 2017), a FOXO4 peptide that perturbs

the FOXO4 interaction with p53 (Baar et al. 2017), CD153 vaccination to remove senescent T cells (Yoshida et al. 2020), etc.

Finally, the role of senescent cell eradication by the immune system (Prata et al. 2018; Kale et al. 2020) and nanomaterial-based delivery systems capable of preferentially killing senescent cells (nano-senolytics) and/or modulating their proinflammatory secretome (nano-senomorphics/nano-senostatics) are areas of active research (Adamczyk-Grochala and Lewinska 2020).

22.5 Gerosuppressors and Senomorphics

Gerosuppressors, also called senomorphics, are compounds or biomedical strategies that suppress, ameliorate, prevent or reverse the senescent state, inhibiting or reducing senescence-inducing triggers such as telomere damage, stress-induced senescence and gene-induced senescence (Martel et al. 2020). Senescent cells exhibit a characteristic secretory profile. This specific secretome is being currently referred to as the "Senescence-associated secretory phenotype" or SASP (Coppe et al. 2008; Kuilman and Peeper 2009). Many different types of compounds and strategies can inhibit or modulate the SASP, including medicines such as statins (Liu et al. 2015), glucocorticoids (Laberge et al. 2012), JAK1/2 inhibitors such as Ruxolitinib (Xu et al. 2015), NF-kB, p38 MAP kinase and MK2 kinase inhibitors (Alimbetov et al. 2016), splicing factor PTBP1 depletion (Georgilis et al. 2018), transgenic cells seeking IL-6 producing senescent cells (Qudrat et al. 2017), etc. Several senomorphic molecules, at an early characterization stage, have been recently presented (Mongelli et al. 2020).

The SASP is important to study because it is the origin of the heightened proinflammatory environment normally found in aged people. Thus, senotherapeutics targeting or modulating the SASP are emerging as alternative therapies to the senolytics (Birch and Gil 2020).

The SASP has been found to be senescence-process specific and cell-type specific, which means that no individual senescent cell would show the exact same secretome profile and the secretome changes over time (Basisty et al. 2020; Schafer et al. 2020).

The senolytic compounds described in Sect. 22.4 can also exert modulation of SASP, to various degrees, and will not be addressed in this section, as their main function is to have senolytic activity.

Below, a list of prominent nutritional gerosuppressors (in alphabetical order) aims to describe their origin, targets and possible uses in senotherapy.

22.5.1 Apigenin

Apigenin (4′,5,7,-trihydroxyflavone) is a flavonoid found in certain herbs, fruits, and vegetables (Cannataro et al. 2021; Jantan et al. 2021). Apigenin has multiple health-promoting effects and therapeutic functions (Salehi et al. 2019; Jantan et al. 2021). It

can inhibit UV-induced cytotoxicity and prevent signs of skin aging in vivo (Choi et al. 2016), Apigenin can attenuate inflammation, which is associated with many chronic diseases of aging. It was shown to strongly inhibit the secretion of IL-6, a prominent cytokine expressed by senescent cells (Laberge et al. 2012). Apigenin suppressed the SASP in three human fibroblast strains induced to senescence by ionizing radiation, constitutive MAPK (mitogen-activated protein kinase) signaling, oncogenic RAS, or replicative exhaustion. The mechanism involves suppression of IL-1α signaling through IRAK1 and IRAK4, p38-MAPK, and NF-κB. Expression and secretion of one SASP factor, CXCL10 (IP10), was strongly inhibited by apigenin. Apigenin is a promising natural product for reducing the impact of senescent cells on age-related diseases such as cancer (Perrott et al. 2017).

Apigenin is an inhibitor of NAD+ase CD38 enzyme (Escande et al. 2013). Declining tissue nicotinamide adenine dinucleotide (NAD) levels are linked to aging and its associated diseases. Pro-inflammatory M1-like macrophages express high levels of the NAD-consuming enzyme CD38 (Covarrubias et al. 2020) and targeting NAD^+ metabolism has emerged as a potential therapeutic approach to ameliorate aging-related disease (Covarrubias et al. 2021).

22.5.2 Avenanthramide

Oats are whole grains that contain several nutrients that modulate directly the innate and adaptive immunity, and indirectly, elicit changes in the gut microbiota and related metabolites (Chen et al. 2021a). One of the oat's nutrients, avenanthramide C (Avn C), was validated as a new senomorphic compound, acting as an inhibitor of SASP and causing a reduction in the levels of markers of senescence. Avn C inhibited the activities of nuclear factor κB (NF-κB) and p38 mitogen-activated protein kinase, and the secretion of inflammatory cytokines. Avn C-induced inhibition of the SASP is triggered by senescence-related stress (Lim et al. 2020).

22.5.3 Epigallocatechin-3-Gallate

Green tea (*Camellia sinesis L.*) is widely known for its anti-cancer and anti-inflammatory properties. Its main antioxidant agents are catechins and derivatives including epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin-3-gallate (EGCG). EGCG has potent health properties, among which is the prevention of several types of cancer (Musial et al. 2020). EGCG is also present in smaller amounts in fruits like apple and plums, onions, hazelnuts, pecans and carob (Haytowitz et al. 2018). EGCG was able to extend the lifespan in obese rats by improving free fatty acids metabolism and reducing the levels of inflammatory molecules and oxidative stress (Yuan et al. 2020). In 3T3-L1 pre-adipocytes, induced to senescence, EGCG could diminish IL-6 protein expression and CDKN1a

(p21) mRNA expression, and increase mitochondrial SIRT3 and NRF2 mRNA expression. SIRT3 activating compounds, such as EGCG, may delay senescence of cells and senescence-induced inflammatory processes (Lilja et al. 2020). EGCG downregulated the PI3K/Akt/mTOR and AMPK signaling pathway and suppressed ROS, iNOS, Cox-2, NF-kB, SASP and p53-mediated cell cycle inhibition in pre-adipocytes, and suppressed the accumulation of anti-apoptotic protein Bcl-2 in senescent cells thereby promoting apoptosis-mediated cell death. EGCG acts as an mTOR inhibitor, SASP modulator as well as a potential senolytic agent thereby indicating its multi-faceted attributes that could be useful for developing anti-aging or age-delaying therapies (Kumar et al. 2019).

22.5.4 Ginsenoside F1

Ginseng has been used as a traditional herb in Asian countries for thousands of years, and contains a large number of active ingredients including steroidal saponins, protopanaxadiols, and protopanaxatriols, collectively known as ginsenosides (Ratan et al. 2021). Ginsenoside F1 is a ginsenoside found in Panax species that grow in the mountainous regions of East Asia. Ginsenoside F1 suppresses the SASP from astrocytes induced by D-galactose via suppressing p38MAPK-dependent NF-κB activity (Hou et al. 2018).

22.5.5 Metformin

Metformin (dimethylbiguanide) has become the preferred first-line oral blood glucose-lowering agent to manage type 2 diabetes. *Galega officinalis* (also known as goat's rue), a traditional herbal medicine in Europe, was found to be rich in guanidine, and shown to lower blood glucose. Guanidine derivatives, including metformin, were synthesized and some (not metformin) were used to treat diabetes in the 1920s and 1930s but were discontinued due to toxicity and the increased availability of insulin (Bailey 2017). Subsequent research led to the discoveries that metformin can improve nutrient sensing, enhance autophagy and intercellular communication, protect against macromolecular damage, delay stem cell aging, modulate mitochondrial function, regulate transcription, and reduce telomere attrition and senescence (Kulkarni et al. 2020). Specifically for aging, metformin leads to decreased insulin levels, decreased IGF-1 signalling, inhibition of mTOR, inhibition of mitochondrial complex 1 in the electron transport chain and reduction of endogenous production of reactive oxygen species (ROS), activation of AMP-activated kinase (AMPK), and reduction in DNA damage (Barzilai et al. 2016) and many more (Morsli and Bellantuono 2021). A large study known as "Targeting aging by metformin" (TAME) is a trial including more than 3000 individuals, ages 65–79, where the effects of metformin on the progression of heart disease, cancer and dementia will be monitored (Kulkarni et al. 2020).

22.5.6 Puerarin

Plants from the genus Pueraria are well known for the health and cosmetic benefits. The medicinally important plants of this genus are commonly known as kudzu, and the predominant phytochemical constituents are isoflavones, also known as phytoestrogens (Wang et al. 2020).

Puerarin (daidzein-8-C-glucoside) is a major isoflavone found in *Pueraria lobata* (Kudzu, Kuzu, Gegen), an edible legume. It possesses a variety of pharmacological actions (Ahmad et al. 2020, Bharti et al. 2020). Tuber and leaf extracts of Pueraria tuberosa contain several bioactive constituents such as daidzein, genistein, quercetin, irisolidone, biochanin A, biochanin B, isoorientin, and mangiferin, which possess an extensive range of pharmacological activities (Bharti et al. 2020). It can prevent the aging-phenotype of human dermal fibroblasts Puerarin blocks aging phenotype in cultured human dermal fibroblasts (Kamiya et al. 2021).

22.5.7 Rapamycin (Sirolimus) and Rapalogues

Rapamycin is not a nutritional gerosuppressor but originates from a natural source. It is one of the most studied senotherapeutics to date. The compound was isolated from *Streptomyces hygroscopicus*, a bacteria found in a soil sample at Rapa Nui, Easter island. Initially, it was known as having antifungal activities (called sirolimus), but later on it was found to have immunosuppressive and antiproliferative properties, so it was used successfully to reduce organ rejection with kidney transplantation. Its roles in cancer suppression led to the discovery that rapamycin is an inhibitor of the mammalian/mechanistic target of rapamycin (mTOR) and is one of the few drugs that is able to extend lifespan in several organisms (Seto 2012, Selvarani et al. 2020). A summary of the in vivo evidence for Rapamycin targeting multiple age-associated dysfunctions and pathologies in mammals has been reviewed (Morsli and Bellantuono 2021).

mTOR is a key component of cellular metabolism that integrates nutrient sensing with cellular processes that fuel cell growth and proliferation, playing a central role in the regulation of the aging process and lifespan (Papadopoli et al. 2019). The effects of rapamycin on various metabolic pathways have been summarized (Morsli and Bellantuono 2021). The low bioavailability of rapamycin led to the design of rapamycin analogues, called "rapalogues", such as mTOR inhibitors temsirolimus (CCI-779), everolimus (RAD001), and ridaforolimus/deforolimus (MK-8669/AP23573), by chemical design. Rapalogues have a safer toxicity profile but still exhibit a number of drawbacks (Viana et al. 2018). Second generation rapalogues, dual mTOR and PI3K inhibitors, mTORC1 and mTORC2 dual inhibitors, have been designed and await further characterization (Leontieva et al. 2015; Zhang et al. 2011). Several polyphenols have been found to inhibit or influence mTOR, such as honokiol, curcumin (see Sect. 22.4.1.2), epigallocatechin-3-gallate (see Sect. 22.5.3), theaflavin digallate,

quercetin (see Sect. 22.4.1.7), punicalagin, fisetin (see Sect. 22.4.1.3), oleoeuropein (see Sect. 22.5.9) and resveratrol (see Sect. 22.5.8) (Pazoki-Toroudi et al. 2016; Kumar et al. 2019).

22.5.8 Resveratrol and Resveralogues

Resveratrol is a non-flavonoid polyphenol stilbenoid (3,5,4′-trihydroxy-*trans*-stilbene) and phytoalexin produced by plants in response to injury e.g. UV or pathogen attack, and is often found in grapes, raisins, berries and peanuts. Resveratrol has the ability to remove ROS, inhibit cyclooxygenase (COX), and trigger anti-inflammatory pathways via SIRT1 activation. Multiple studies show that resveratrol can suppress SASP. However, lifespan extension has yet not been confirmed (Grinan-Ferre et al. 2021).

Epigenetic modifications are associated with genome stability, gene transcription, and metabolic regulation. Acetylation is one of the most characterized histone modifications. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes control the levels of histone acetylation, modulating gene expression (Cavalli and Heard 2019). Sirtuins (SIRT) 1–7 are enzymes classified as class III HDACs.

A recent work presented ongoing clinical trials using resveratrol as well as other phytochemicals stimulating SIRT1 activity (Iside et al. 2020). The parent resveratrol molecule has been modified to give rise to at least 24 different "resveralogues", structurally related to resveratrol. Replacement of the 3,5-dihydroxy substituents with 3,5-dimethoxy groups significantly enhances SIRT1 activity, and reduces toxicity. At 100 μM many of the compounds, including resveratrol, induce senescence in primary human fibroblast MRC5 cells in culture. However, at lower concentrations (10 μM), most compounds rescued subpopulations of cells within the culture from senescence (Birar et al. 2020).

22.5.9 Secoiridoids

Iridoids are cyclopentane [c] pyran monoterpenoids present in plants and insects, considered as defensive compounds. Cleavage of a bond in the cyclopentane ring leads to the formation of a subclass known as secoiridoids, bioactive compounds with a large variety of pharmacological properties including anti-diabetic, anti-inflammatory, immunosuppressive, neuroprotective, anti-cancer and anti-obesity. The olive tree *Olea europaea L.* is particularly rich in oleuropein (OL), dimethyl-OL, and ligstroside secoiridoids, and their hydrolysis derivatives are mostly OL-aglycone, oleocanthal (OLE), oleacein (OLA), elenolate, oleoside-11-methyl ester, elenoic acid, hydroxytyrosol (HTy), and tyrosol (Ty) (Castejon et al. 2020). The presence of OLE and OLA in extra-virgin olive oil has been investigated in relation to healthy aging (Nikou et al. 2019). OLE and ligstroside have been found to protect

against mitochondrial dysfunction in models of Alzheimer's disease and brain aging (Grewal et al. 2020).

22.6 Other Nutritional and Dietary Interventions

22.6.1 Geroprotectors

Many natural products do not necessarily fall into the categories of senolytics and gerosuppressors per se, but exert their health-promoting and anti-aging activities as contributors to protect cellular integrity. A geroprotector is a compound that protects the integrity of cellular structures and macromolecules. Several gerosuppressors that modulate the SASP can also act as geroprotectors, such as rapamycin and metformin (Morsli and Bellantuono 2021).

Nutraceutical compounds encompassing phytochemicals, probiotic bacteria and omega-3-fatty acids have shown promising anti-immunosenescence and anti-cellular senescence potential in immune cell (Sharma and Padwad 2020).

There are many nutritional anti-aging compounds**.** Anti-carcinogenic, anti-inflammatory, anti-viral, anti-microbial, anti-proliferative and antioxidant activities can be found in many phytochemicals, that either directly or indirectly can be considered geroprotective. Examples are found in the Citrus family (oranges, lemons, grapefruits, etc.) (Barreca et al. 2020), foods in the Mediterranean diet (Cannataro et al. 2021), edible flowers (Zheng et al. 2021), honey (Jaganathan and Mandal 2009), olive oils (Nikou et al. 2019), mushrooms (Abdelshafy et al. 2021), cocoa (Martin and Ramos 2021), etc.

Alpha-ketoglutarate (AKG), an intermediate of the tricarboxylic acid cycle that leads to energy production, biosynthesis of certain amino acids, collagen biosynthesis, epigenetic regulation of gene expression, regulation of redox homeostasis, and detoxification of hazardous substances, can extend lifespan and delay the onset of age-associated decline in experimental animal models, and is being considered a geroprotective drug (Bayliak and Lushchak 2021).

Nicotinamide (NAM) is a form of vitamin B_3 found mainly in meat, fish, cereals, nuts, and mushrooms, as well as to a lesser extent in some vegetables and used as a dietary supplement and medication. Nicotinamide mononucleotide (NMN) is a nucleotide derivative of niacin (one of three forms of vitamin B_3). NMN is a precursor of NAD+, an important cofactor in redox reactions in energy metabolism. Aging is accompanied by a gradual decline in tissue and cellular NAD^+ levels in multiple model organisms, including rodents and humans. Therefore, supplementation with NMN is geroprotective (Covarrubias et al. 2021).

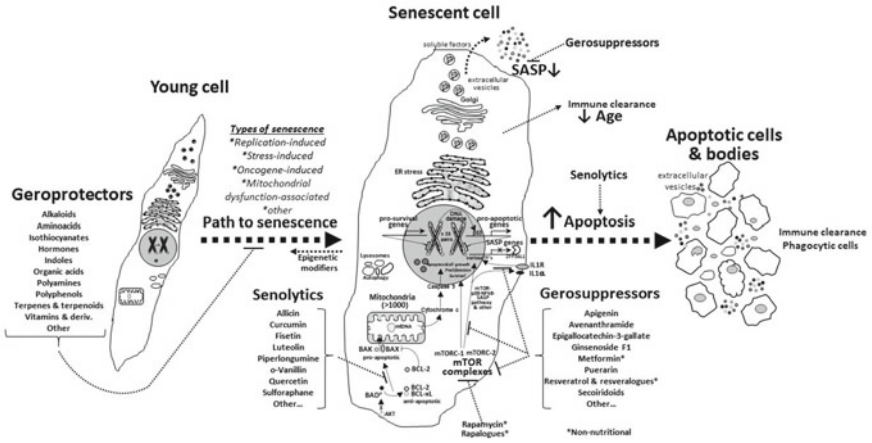

Fig. 22.1 Schematic representation of the main modes of action of several nutritional senolytic compounds and gerosuppressors on senescent cells. Nutritional compounds may have multiple targets and multiple functions. The specific senescent state can vary from one cell to another, and can also vary between cell/tissue types. A nutritional senotherapeutic may have different effects depending on the specific type of senescent cell. Abbreviations: mTOR (mammalian/mechanistic target of rapamycin), SASP (Senescence-associated secretory phenotype). The full name and description of genes and proteins can be found in https://www.genecards.org/

22.6.2 Epigenetic Modifiers

Very few studies have yet explored the role of specific nutrients in epigenetic modification to achieve rejuvenation as a means of anti-aging strategies. One recent study has shown that a 1-year Mediterranean-like diet, in a pilot study of elderly healthy subjects from the NU-AGE study (60 Italians, 60 Poles), resulted in epigenetic rejuvenation (Gensous et al. 2020).

In the trial "Thymus Regeneration, Immunorestoration, and Insulin Mitigation" (TRIIM), nine healthy men were given a cocktail of human growth hormone (hGH), metformin, dehydroepidandrosterone (DHEA), vitamin D3, and zinc for 1-year, that shed about 2.5 years off their biological ages, according to an analysis of their epigenome. (Fahy et al. 2019; Bartke et al. 2021) (Fig. 22.1).

22.7 Concluding Remarks and Future Perspectives

The nutritional geroscience field is relatively young. The impact that pharmacologically-synthesized senomorphics and dietary components, alone or in combination, might have on the short- and long-term survival and secretory function of senescent cells awaits further characterization. The cellular and systemic

divergence of phytochemical targets suggests that the best way to assess the contribution of individual nutrients or compounds, alone or in combination, is to design long-term longitudinal clinical trials, whereby individuals of different genetic backgrounds, lifestyles and environments, are followed to assess health outcomes, disease emergence, duration of health span and lifespan.

Senescent cells arise by means of different processes, and their resulting SASP profiles will undoubtedly be heterogenous. It is therefore expected that their response to senolytics and senomorphic compounds will vary. Clinical intervention studies will be needed to understand the precise contribution of single or combined dietary phytochemicals, to the rate of aging in each one of the aging trajectories that lead to specific age-associated diseases and their accompanying disabilities.

It is becoming more evident that most of the compounds tested to date, that have anti-senescence phenotype properties, have multiple targets, and their use might influence cells and body processes other than only senescent cells. This implies that safety issues need to always be considered when administering senotherapeutics, including estimation of the senescence burden of an individual before any clinical intervention.

The significance of hormesis to the use of senotherapeutics will require understanding the effects of different doses, frequency and time of administration (Santoro et al. 2020; Rattan 2008).

The list of natural compounds that can exert senolytic and senomorphic activities is likely to grow in the years to come, some of which could have novel targets on pre-senescent and senescent cells. It is important to assess the chemical structure of the natural compound including its modifications such as glycosylation, etc. that could have implications for their activities in vivo, implying that chemical synthesis of the basic structure of the compounds alone may not be sufficient to result in fully active senotherapeutics (Huang et al. 2016).

Finally, it would be ideal to investigate the role of natural and synthetic compounds on non-senescent cells, at all stages of their lives, that could help to delay senescence and improve resilience, without significantly compromising basic body function. The pursuit of an extended health span by means of dietary interventions would facilitate health care and reduce or postpone disease burden among the elderly.

Acknowledgements I wish to thank Juliette Tavenier and Ove Andersen for stimulating discussions. The author wishes to acknowledge the contributions of many nutrition researchers, about the role of nutritional factors on health and aging, that could not be included here due to space limitations.

Compliance with Ethical Standards

Funding The support from Amager and Hvidovre- Copenhagen University hospital is gratefully acknowledged.

Conflict of Interest I have no conflict of interests to report.

References

Abdelshafy AM, Belwal T, Liang Z, Wang L, Li D, Luo Z, Li L (2021) A comprehensive review on phenolic compounds from edible mushrooms: Occurrence, biological activity, application and future prospective. Crit Rev Food Sci Nutr. https://doi.org/10.1080/10408398.2021.1898335. Online ahead of print

Adamczyk-Grochala J, Lewinska A (2020) Nano-based theranostic tools for the detection and elimination of senescent cells. Cells 9:2659

Ahmad B, Khan S, Liu Y, Xue M, Nabi G, Kumar S, Alshwmi M, Qarluq AW (2020) Molecular mechanisms of anticancer activities of puerarin. Cancer Manag Res 12:79–90

Alimbetov D, Davis T, Brook AJ, Cox LS, Faragher RG, Nurgozhin T, Zhumadilov Z, Kipling D (2016) Suppression of the senescence-associated secretory phenotype (SASP) in human fibroblasts using small molecule inhibitors of p38 MAP kinase and MK2. Biogerontology 17:305–315

Ansary J, Forbes-Hernandez TY, Gil E, Cianciosi D, Zhang J, Elexpuru-Zabaleta M, Simal-Gandara J, Giampieri F, Battino M (2020) Potential health benefit of garlic based on human intervention studies: a brief overview. Antioxidants (Basel) 9:619

Baar MP, Brandt RMC, Putavet DA, Klein JDD, Derks KWJ, Bourgeois BRM, Stryeck S, Rijksen Y, Van Willigenburg H, Feijtel DA, Van Der Pluijm I, Essers J, Van Cappellen WA, Van IWF, Houtsmuller AB, Pothof J, De Bruin RWF, Madl T, Hoeijmakers JHJ, Campisi J, De Keizer PLJ (2017) Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell 169:132–147.e16

Bailey CJ (2017) Metformin: historical overview. Diabetologia 60:1566–1576

Barreca D, Mandalari G, Calderaro A, Smeriglio A, Trombetta D, Felice MR, Gattuso G (2020) Citrus flavones: an update on sources, biological functions, and health promoting properties. Plants (Basel) 9:288

Barrera-Vazquez OS, Gomez-Verjan JC, Magos-Guerrero GA (2021) Chemoinformatic screening for the selection of potential senolytic compounds from natural products. Biomolecules 11:467

Bartke A, Hascup E, Hascup K, Masternak MM (2021) Growth hormone and aging: new findings. World J Mens Health 39:454–465

Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA (2016) Metformin as a tool to target aging. Cell Metab 23:1060–1065

Basisty N, Kale A, Jeon OH, Kuehnemann C, Payne T, Rao C, Holtz A, Shah S, Sharma V, Ferrucci L, Campisi J, Schilling B (2020) A proteomic atlas of senescence-associated secretomes for aging biomarker development. PLoS Biol 18:e3000599

Batiha GE, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, Algammal AM, Elewa YHA (2020) The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. Foods 9:374

Bayliak MM, Lushchak VI (2021) Pleiotropic effects of alpha-ketoglutarate as a potential anti-ageing agent. Ageing Res Rev 66:101237

Bezerra DP, Pessoa C, de Moraes MO, Saker-Neto N, Silveira ER, Costa-Lotufo LV (2013) Overview of the therapeutic potential of piplartine (piperlongumine). Eur J Pharm Sci 48:453–463

Bharti R, Chopra BS, Raut S, Khatri N (2020) Pueraria tuberosa: a review on traditional uses, pharmacology, and phytochemistry. Front Pharmacol 11:582506

Bian Y, Wei J, Zhao C, Li G (2020) Natural polyphenols targeting senescence: a novel prevention and therapy strategy for cancer. Int J Mol Sci 21:684

Bielak-Zmijewska A, Grabowska W, Ciolko A, Bojko A, Mosieniak G, Bijoch L, Sikora E (2019) The role of curcumin in the modulation of ageing. Int J Mol Sci 20:1239

Birar VC, Sheerin AN, Ostler EL, Faragher RGA (2020) Novel resveratrol derivatives have diverse effects on the survival, proliferation and senescence of primary human fibroblasts. Biogerontology 21:817–826

Birch J, Gil J (2020) Senescence and the SASP: many therapeutic avenues. Genes Dev 34:1565–1576

Borlinghaus J, Foerster Nee Reiter J, Kappler U, Antelmann H, Noll U, Gruhlke MCH, Slusarenko AJ (2021) Allicin, the odor of freshly crushed garlic: a review of recent progress in understanding Allicin's effects on cells. Molecules 26(6):1505

Bussian TJ, Aziz A, Meyer CF, Swenson BL, van Deursen JM, Baker DJ (2018) Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. Nature 562:578–582

Cai Y, Zhou H, Zhu Y, Sun Q, Ji Y, Xue A, Wang Y, Chen W, Yu X, Wang L, Chen H, Li C, Luo T, Deng H (2020) Elimination of senescent cells by beta-galactosidase-targeted prodrug attenuates inflammation and restores physical function in aged mice. Cell Res 30:574–589

Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A (2019) Cellular senescence: aging, cancer, and injury. Physiol Rev 99:1047–1078

Cannataro R, Fazio A, la Torre C, Caroleo MC, Cione E (2021) Polyphenols in the Mediterranean diet: from dietary sources to microRNA modulation. Antioxidants (Basel) 10:328

Castejon ML, Montoya T, Alarcon-de-la-Lastra C, Sanchez-Hidalgo M (2020) Potential protective role exerted by secoiridoids from Olea europaea L. in cancer, cardiovascular, neurodegenerative, aging-related, and immunoinflammatory diseases. Antioxidants (Basel) 9(2):149

Cavalcante MB, Saccon TD, Nunes ADC, Kirkland JL, Tchkonia T, Schneider A, Masternak MM (2020) Dasatinib plus quercetin prevents uterine age-related dysfunction and fibrosis in mice. Aging (Albany NY) 12:2711–2722

Cavalli G, Heard E (2019) Advances in epigenetics link genetics to the environment and disease. Nature 571(7766):489–499

Chandra A, Lagnado AB, Farr JN, Monroe DG, Park S, Hachfeld C, Tchkonia T, Kirkland JL, Khosla S, Passos JF, Pignolo RJ (2020) Targeted reduction of senescent cell burden alleviates focal radiotherapy-related bone loss. J Bone Miner Res 35:1119–1131

Chen O, Mah E, Dioum E, Marwaha A, Shanmugam S, Malleshi N, Sudha V, Gayathri R, Unnikrishnan R, Anjana RM, Krishnaswamy K, Mohan V, Chu Y (2021a) The role of oat nutrients in the immune system: a narrative review. Nutrients 13(4):1048

Chen XK, Yi ZN, Wong GT, Hasan KMM, Kwan JS, Ma AC, Chang RC (2021b) Is exercise a senolytic medicine? A systematic review. Aging Cell 20(1):e13294

Cherif H, Bisson DG, Jarzem P, Weber M, Ouellet JA, Haglund L (2019) Curcumin and o-Vanillin exhibit evidence of senolytic activity in human IVD cells in vitro. J Clin Med 8:433

Cherif H, Bisson DG, Mannarino M, Rabau O, Ouellet JA, Haglund L (2020) Senotherapeutic drugs for human intervertebral disc degeneration and low back pain. Elife 9:e54693

Childs BG, Gluscevic M, Baker DJ, Laberge RM, Marquess D, Dananberg J, van Deursen JM (2017) Senescent cells: an emerging target for diseases of ageing. Nat Rev Drug Discov 16:718–735

Choi S, Youn J, Kim K, Da Joo H, Shin S, Lee J, Lee HK, An IS, Kwon S, Youn HJ, Ahn KJ, An S, Cha HJ (2016) Apigenin inhibits UVA-induced cytotoxicity in vitro and prevents signs of skin aging in vivo. Int J Mol Med 38:627–34

Constantin RP, Constantin J, Pagadigorria CL, Ishii-Iwamoto EL, Bracht A, de Castro CV, Yamamoto NS (2011) Prooxidant activity of fisetin: effects on energy metabolism in the rat liver. J Biochem Mol Toxicol 25:117–126

Conti P, Caraffa A, Gallenga CE, Ross R, Kritas SK, Frydas I, Younes A, di Emidio P, Ronconi G, Pandolfi F (2021) Powerful anti-inflammatory action of luteolin: potential increase with IL-38. Biofactors 47:165–169

Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6:2853–2868

Covarrubias AJ, Kale A, Perrone R, Lopez-Dominguez JA, Pisco AO, Kasler HG, Schmidt MS, Heckenbach I, Kwok R, Wiley CD, Wong HS, Gibbs E, Iyer SS, Basisty N, Wu Q, Kim IJ, Silva E, Vitangcol K, Shin KO, Lee YM, Riley R, Ben-Sahra I, Ott M, Schilling B, Scheibye-Knudsen M, Ishihara K, Quake SR, Newman J, Brenner C, Campisi J, Verdin E (2020) Senescent cells promote tissue NAD(+) decline during ageing via the activation of CD38(+) macrophages. Nat Metab 2:1265–1283

Covarrubias AJ, Perrone R, Grozio A, Verdin E (2021) NAD(+) metabolism and its roles in cellular processes during ageing. Nat Rev Mol Cell Biol 22:119–141

Dai H, Chen R, Gui C, Tao T, Ge Y, Zhao X, Qin R, Yao W, Gu S, Jiang Y, Gui J (2020) Eliminating senescent chondrogenic progenitor cells enhances chondrogenesis under intermittent hydrostatic pressure for the treatment of OA. Stem Cell Res Ther 11:199

di Micco R, Krizhanovsky V, Baker D, D'adda di Fagagna F (2021) Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol 22(2):75–95

Dookun E, Passos JF, Arthur HM, Richardson GD (2020a) Therapeutic potential of senolytics in cardiovascular disease. Cardiovasc Drugs Ther. https://doi.org/10.1007/s10557-020-07075-w. Online ahead of print

Dookun E, Walaszczyk A, Redgrave R, Palmowski P, Tual-Chalot S, Suwana A, Chapman J, Jirkovsky E, Donastorg Sosa L, Gill E, Yausep OE, Santin Y, Mialet-Perez J, Andrew Owens W, Grieve D, Spyridopoulos I, Taggart M, Arthur HM, Passos JF, Richardson GD (2020b) Clearance of senescent cells during cardiac ischemia-reperfusion injury improves recovery. Aging Cell 19(10):e13249

Escande C, Nin V, Price NL, Capellini V, Gomes AP, Barbosa MT, O'Neil L, White TA, Sinclair DA, Chini EN (2013) Flavonoid apigenin is an inhibitor of the NAD+ ase CD38: implications for cellular NAD+ metabolism, protein acetylation, and treatment of metabolic syndrome. Diabetes 62:1084–1093

Fahy GM, Brooke RT, Watson JP, Good Z, Vasanawala SS, Maecker H, Leipold MD, Lin DTS, Kobor MS, Horvath S (2019) Reversal of epigenetic aging and immunosenescent trends in humans. Aging Cell 18:e13028

Farr JN, Xu M, Weivoda MM, Monroe DG, Fraser DG, Onken JL, Negley BA, Sfeir JG, Ogrodnik MB, Hachfeld CM, Lebrasseur NK, Drake MT, Pignolo RJ, Pirtskhalava T, Tchkonia T, Oursler MJ, Kirkland JL, Khosla S (2017) Targeting cellular senescence prevents age-related bone loss in mice. Nat Med 23:1072–1079

Fragkou PC, Karaviti D, Zemlin M, Skevaki C (2021) Impact of early life nutrition on children's immune system and noncommunicable diseases through its effects on the bacterial microbiome, virome and mycobiome. Front Immunol 12:644269

Fuhrmann-Stroissnigg H, Ling YY, Zhao J, McGowan SJ, Zhu Y, Brooks RW, Grassi D, Gregg SQ, Stripay JL, Dorronsoro A, Corbo L, Tang P, Bukata C, Ring N, Giacca M, Li X, Tchkonia T, Kirkland JL, Niedernhofer LJ, Robbins PD (2017) Identification of HSP90 inhibitors as a novel class of senolytics. Nat Commun 8:422

Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH, Mantovani A, Weyand CM, Barzilai N, Goronzy JJ, Rando TA, Effros RB, Lucia A, Kleinstreuer N, Slavich GM (2019) Chronic inflammation in the etiology of disease across the life span. Nat Med 25:1822–1832

Gendrisch F, Esser PR, Schempp CM, Wolfle U (2020) Luteolin as a modulator of skin aging and inflammation. Biofactors 47:170–180

Gensous N, Garagnani P, Santoro A, Giuliani C, Ostan R, Fabbri C, Milazzo M, Gentilini D, di Blasio AM, Pietruszka B, Madej D, Bialecka-Debek A, Brzozowska A, Franceschi C, Bacalini MG (2020) One-year Mediterranean diet promotes epigenetic rejuvenation with country- and sex-specific effects: a pilot study from the NU-AGE project. Geroscience 42:687–701

Georgilis A, Klotz S, Hanley CJ, Herranz N, Weirich B, Morancho B, Leote AC, D'Artista L, Gallage S, Seehawer M, Carroll T, Dharmalingam G, Wee KB, Mellone M, Pombo J, Heide D, Guccione E, Arribas J, Barbosa-Morais NL, Heikenwalder M, Thomas GJ, Zender L, Gil J (2018) PTBP1-mediated alternative splicing regulates the inflammatory secretome and the pro-tumorigenic effects of senescent cells. Cancer Cell 34:85–1029

Grewal R, Reutzel M, Dilberger B, Hein H, Zotzel J, Marx S, Tretzel J, Sarafeddinov A, Fuchs C, Eckert GP (2020) Purified oleocanthal and ligstroside protect against mitochondrial dysfunction in models of early Alzheimer's disease and brain ageing. Exp Neurol 328:113248

Grinan-Ferre C, Bellver-Sanchis A, Izquierdo V, Corpas R, Roig-Soriano J, Chillon M, Andres-Lacueva C, Somogyvari M, Soti C, Sanfeliu C, Pallas M (2021) The pleiotropic neuroprotective

effects of resveratrol in cognitive decline and Alzheimer's disease pathology: from antioxidant to epigenetic therapy. Ageing Res Rev 67:101271
Grynkiewicz G, Demchuk OM (2019) New perspectives for fisetin. Front Chem 7:697
Guerrero A, Guiho R, Herranz N, Uren A, Withers DJ, Martinez-Barbera JP, Tietze LF, Gil J (2020) Galactose-modified duocarmycin prodrugs as senolytics. Aging Cell 19:e13133
Hachmo Y, Hadanny A, Abu Hamed R, Daniel-Kotovsky M, Catalogna M, Fishlev G, Lang E, Polak N, Doenyas K, Friedman M, Zemel Y, Bechor Y, Efrati S (2020) Hyperbaric oxygen therapy increases telomere length and decreases immunosenescence in isolated blood cells: a prospective trial. Aging (Albany NY) 12:22445–22456
Haytowitz DB, Wu X, Bhagwat S (2018) USDA Database for the Flavonoid Content of Selected Foods. Agricultural Research Service, U.S. Department of Agriculture, Nutrient Data Laboratory, Release 3.3, March 2018. https://www.ars.usda.gov/ARSUserFiles/80400535/Data/Flav/Flav3.3.pdf
Henrique T, Zanon CF, Girol AP, Stefanini ACB, Contessoto NSA, da Silveira NJF, Bezerra DP, Silveira ER, Barbosa-Filho JM, Cornelio ML, Oliani SM, Tajara EH (2020) Biological and physical approaches on the role of piplartine (piperlongumine) in cancer. Sci Rep 10:22283
Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D (1993) Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen elderly study. Lancet 342:1007–1011
Hickson LJ, Langhi Prata LGP, Bobart SA, Evans TK, Giorgadze N, Hashmi SK, Herrmann SM, Jensen MD, Jia Q, Jordan KL, Kellogg TA, Khosla S, Koerber DM, Lagnado AB, Lawson DK, Lebrasseur NK, Lerman LO, Mcdonald KM, Mckenzie TJ, Passos JF, Pignolo RJ, Pirtskhalava T, Saadiq IM, Schaefer KK, Textor SC, Victorelli SG, Volkman TL, Xue A, Wentworth MA, Wissler Gerdes EO, Zhu Y, Tchkonia T, Kirkland JL (2019) Senolytics decrease senescent cells in humans: preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. EBioMedicine 47:446–456
Hou J, Cui C, Kim S, Sung C, Choi C (2018) Ginsenoside F1 suppresses astrocytic senescence-associated secretory phenotype. Chem Biol Interact 283:75–83
Huang G, Lv M, Hu J, Huang K, Xu H (2016) Glycosylation and activities of natural products. Mini Rev Med Chem 16:1013–1016
Iside C, Scafuro M, Nebbioso A, Altucci L (2020) SIRT1 activation by natural phytochemicals: an overview. Front Pharmacol 11:1225
Jaganathan SK, Mandal M (2009) Antiproliferative effects of honey and of its polyphenols: a review. J Biomed Biotechnol 2009:830616
Jantan I, Haque MA, Arshad L, Harikrishnan H, Septama AW, Mohamed-Hussein ZA (2021) Dietary polyphenols suppress chronic inflammation by modulation of multiple inflammation-associated cell signaling pathways. J Nutr Biochem 93:108634
Jeon OH, Kim C, Laberge RM, Demaria M, Rathod S, Vasserot AP, Chung JW, Kim DH, Poon Y, David N, Baker DJ, van Deursen JM, Campisi J, Elisseeff JH (2017) Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med 23:775–781
Justice JN, Nambiar AM, Tchkonia T, Lebrasseur NK, Pascual R, Hashmi SK, Prata L, Masternak MM, Kritchevsky SB, Musi N, Kirkland JL (2019) Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study. EBioMedicine 40:554–563
Kale A, Sharma A, Stolzing A, Desprez PY, Campisi J (2020) Role of immune cells in the removal of deleterious senescent cells. Immun Ageing 17:16
Kamiya Y, Odama M, Mizuguti A, Murakami S, Ito T (2021) Puerarin blocks aging phenotype in cultured human dermal fibroblasts. PLoS One 16(4):e0249367
Kashyap D, Garg VK, Tuli HS, Yerer MB, Sak K, Sharma AK, Kumar M, Aggarwal V, Sandhu SS (2019) Fisetin and quercetin: promising flavonoids with chemopreventive potential. Biomolecules 9:174
Khaltourina D, Matveyev Y, Alekseev A, Cortese F, Iovita A (2020) Aging fits the disease criteria of the international classification of diseases. Mech Ageing Dev 189:111230

Kirkland JL, Tchkonia T (2020) Senolytic drugs: from discovery to translation. J Intern Med 288:518–536
Kubo C, Ogawa M, Uehara N, Katakura Y (2020) Fisetin promotes hair growth by augmenting TERT expression. Front Cell Dev Biol 8:566617
Kuilman T, Peeper DS (2009) Senescence-messaging secretome: SMS-ing cellular stress. Nat Rev Cancer 9:81–94
Kulkarni AS, Gubbi S, Barzilai N (2020) Benefits of metformin in attenuating the hallmarks of aging. Cell Metab 32:15–30
Kumar R, Sharma A, Kumari A, Gulati A, Padwad Y, Sharma R (2019) Epigallocatechin gallate suppresses premature senescence of preadipocytes by inhibition of PI3K/Akt/mTOR pathway and induces senescent cell death by regulation of Bax/Bcl-2 pathway. Biogerontology 20:171–189
Laberge RM, Zhou L, Sarantos MR, Rodier F, Freund A, de Keizer PL, Liu S, Demaria M, Cong YS, Kapahi P, Desprez PY, Hughes RE, Campisi J (2012) Glucocorticoids suppress selected components of the senescence-associated secretory phenotype. Aging Cell 11:569–578
Lammermann I, Terlecki-Zaniewicz L, Weinmullner R, Schosserer M, Dellago H, De Matos Branco AD, Autheried D, Sevcnikar B, Kleissl L, Berlin I, Morizot F, Lejeune F, Fuzzati N, Forestier S, Toribio A, Tromeur A, Weinberg L, Higareda Almaraz JC, Scheideler M, Rietveld M, El Ghalbzouri A, Tschachler E, Gruber F, Grillari J (2018) Blocking negative effects of senescence in human skin fibroblasts with a plant extract. NPJ Aging Mech Dis 4:4
Lee KS, Lin S, Copland DA, Dick AD, Liu J (2021) Cellular senescence in the aging retina and developments of senotherapies for age-related macular degeneration. J Neuroinflammation 18:32
Leontieva OV, Demidenko ZN, Blagosklonny MV (2015) Dual mTORC1/C2 inhibitors suppress cellular geroconversion (a senescence program). Oncotarget 6:23238–23248
Leri M, Scuto M, Ontario ML, Calabrese V, Calabrese EJ, Bucciantini M, Stefani M (2020) Healthy effects of plant polyphenols: molecular mechanisms. Int J Mol Sci 21:1250
Lewinska A, Adamczyk-Grochala J, Deregowska A, Wnuk M (2017) Sulforaphane-induced cell cycle arrest and senescence are accompanied by DNA hypomethylation and changes in microRNA profile in breast cancer cells. Theranostics 7:3461–3477
Li C, Shen Y, Huang L, Liu C, Wang J (2021) Senolytic therapy ameliorates renal fibrosis postacute kidney injury by alleviating renal senescence. FASEB J 35:e21229
Li R, Zhang X, Tian X, Shen C, Zhang Q, Zhang Y, Wang Z, Wang F, Tao Y (2017) Triptolide inhibits tumor growth by induction of cellular senescence. Oncol Rep 37:442–448
Li W, He Y, Zhang R, Zheng G, Zhou D (2019) The curcumin analog EF24 is a novel senolytic agent. Aging (Albany NY) 11:771–782
Lilja S, Oldenburg J, Pointner A, Dewald L, Lerch M, Hippe B, Switzeny O, Haslberger A (2020) Epigallocatechin gallate effectively affects senescence and anti-SASP via SIRT3 in 3T3-L1 preadipocytes in comparison with other bioactive substances. Oxid Med Cell Longev 2020:4793125
Lim JS, Lee DY, Kim HS, Park SC, Park JT, Kim HS, Oh WK, Cho KA (2020) Identification of a novel senomorphic agent, avenanthramide C, via the suppression of the senescence-associated secretory phenotype. Mech Ageing Dev 192:111355
Liu S, Uppal H, Demaria M, Desprez PY, Campisi J, Kapahi P (2015) Simvastatin suppresses breast cancer cell proliferation induced by senescent cells. Sci Rep 5:17895
Malavolta M, Bracci M, Santarelli L, Sayeed MA, Pierpaoli E, Giacconi R, Costarelli L, Piacenza F, Basso A, Cardelli M, Provinciali M (2018) Inducers of Senescence, toxic compounds, and senolytics: the multiple faces of Nrf2-activating phytochemicals in cancer adjuvant therapy. Mediators Inflamm 2018:4159013
Mansoori S, Dini A, Chai SC (2021) Effects of tart cherry and its metabolites on aging and inflammatory conditions: efficacy and possible mechanisms. Ageing Res Rev 66:101254
Martel J, Ojcius DM, Wu CY, Peng HH, Voisin L, Perfettini JL, Ko YF, Young JD (2020) Emerging use of senolytics and senomorphics against aging and chronic diseases. Med Res Rev 40:2114–2131

Martin MA, Ramos S (2021) Impact of cocoa flavanols on human health. Food Chem Toxicol 151:112121
Martin N, Huna A, Bernard D (2021) Elimination of senescent endothelial cells: good or bad idea? Trends Cell Biol 5:327–330
Martin N, Soriani O, Bernard D (2020) Cardiac glycosides as senolytic compounds. Trends Mol Med 26:243–245
Marton A, Kusz E, Kolozsi C, Tubak V, Zagotto G, Buzas K, Quintieri L, Vizler C (2016) Vanillin analogues o-Vanillin and 2,4,6-trihydroxybenzaldehyde inhibit NFkB activation and suppress growth of A375 human melanoma. Anticancer Res 36:5743–5750
Mehta P, Pawar A, Mahadik K, Bothiraja C (2018) Emerging novel drug delivery strategies for bioactive flavonol fisetin in biomedicine. Biomed Pharmacother 106:1282–1291
Mongelli A, Atlante S, Barbi V, Bachetti T, Martelli F, Farsetti A, Gaetano C (2020) Treating senescence like cancer: novel perspectives in senotherapy of chronic diseases. Int J Mol Sci 21:7984
Morsli S, Bellantuono I (2021) The use of geroprotectors to prevent multimorbidity: opportunities and challenges. Mech Ageing Dev 193:111391
Mukherjee PK, Harwansh RK, Bahadur S, Banerjee S, Kar A, Chanda J, Biswas S, Ahmmed SM, Katiyar CK (2017) Development of Ayurveda - tradition to trend. J Ethnopharmacol 197:10–24
Musial C, Kuban-Jankowska A, Gorska-Ponikowska M (2020) Beneficial properties of green tea catechins. Int J Mol Sci 21:1744
Nikou T, Liaki V, Stathopoulos P, Sklirou AD, Tsakiri EN, Jakschitz T, Bonn G, Trougakos IP, Halabalaki M, Skaltsounis LA (2019) Comparison survey of EVOO polyphenols and exploration of healthy aging-promoting properties of oleocanthal and oleacein. Food Chem Toxicol 125:403–412
Nogueira-Recalde U, Lorenzo-Gomez I, Blanco FJ, Loza MI, Grassi D, Shirinsky V, Shirinsky I, Lotz M, Robbins PD, Dominguez E, Carames B (2019) Fibrates as drugs with senolytic and autophagic activity for osteoarthritis therapy. EBioMedicine 45:588–605
Paez-Ribes M, Gonzalez-Gualda E, Doherty GJ, Munoz-Espin D (2019) Targeting senescent cells in translational medicine. EMBO Mol Med 11:e10234
Palmer AK, Tchkonia T, Kirkland JL (2021) Senolytics: potential for alleviating diabetes and its complications. Endocrinology 162:bqab058
Papadopoli D, Boulay K, Kazak L, Pollak M, Mallette F, Topisirovic I, Hulea L (2019) mTOR as a central regulator of lifespan and aging. F1000Res 8 (F1000 Fac Rev):998:1–21
Pazoki-Toroudi H, Amani H, Ajami M, Nabavi SF, Braidy N, Kasi PD, Nabavi SM (2016) Targeting mTOR signaling by polyphenols: a new therapeutic target for ageing. Ageing Res Rev 31:55–66
Perrott KM, Wiley CD, Desprez PY, Campisi J (2017) Apigenin suppresses the senescence-associated secretory phenotype and paracrine effects on breast cancer cells. Geroscience 39:161–173
Picallos-Rabina P, Da Silva-Álvarez S, Antelo-Iglesias L, Triana-Martínez F, Collado M (2020) Senotherapy of cancer. In: Muñoz-Espin D, Demaria M (eds) Senolytics in disease, ageing and longevity. Springer, pp. 85-99. ISBN 978-3-030-44903-2
Prasanna PG, Citrin DE, Hildesheim J, Ahmed MM, Venkatachalam S, Riscuta G, Xi D, Zheng G, Van Deursen J, Goronzy J, Kron SJ, Anscher MS, Sharpless NE, Campisi J, Brown SL, Niedernhofer LJ, O'loghlen A, Georgakilas AG, Paris F, Gius D, Gewirtz DA, Schmitt CA, Abazeed ME, Kirkland JL, Richmond A, Romesser PB, Lowe SW, Gil J, Mendonca MS, Burma S, Zhou D, Coleman CN (2021) Therapy-induced senescence: opportunities to improve anti-cancer therapy. J Natl Cancer Inst, djab064. https://doi.org/10.1093/jnci/djab064. Online ahead of print
Prata L, Ovsyannikova IG, Tchkonia T, Kirkland JL (2018) Senescent cell clearance by the immune system: emerging therapeutic opportunities. Semin Immunol 40:101275
Quach A, Levine ME, Tanaka T, Lu AT, Chen BH, Ferrucci L, Ritz B, Bandinelli S, Neuhouser ML, Beasley JM, Snetselaar L, Wallace RB, Tsao PS, Absher D, Assimes TL, Stewart JD, Li Y,

Hou L, Baccarelli AA, Whitsel EA, Horvath S (2017) Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. Aging (Albany NY) 9:419–446
Qudrat A, Wong J, Truong K (2017) Engineering mammalian cells to seek senescence-associated secretory phenotypes. J Cell Sci 130:3116–3123
Raffaele M, Kovacovicova K, Frohlich J, Lo Re O, Giallongo S, Oben JA, Faldyna M, Leva L, Giannone AG, Cabibi D, Vinciguerra M (2021) Mild exacerbation of obesity- and age-dependent liver disease progression by senolytic cocktail dasatinib + quercetin. Cell Commun Signal 19:44
Ratan ZA, Haidere MF, Hong YH, Park SH, Lee JO, Lee J, Cho JY (2021) Pharmacological potential of ginseng and its major component ginsenosides. J Ginseng Res 45:199–210
Rattan SI (2008) Hormesis in aging. Ageing Res Rev 7:63–78
Robbins PD, Jurk D, Khosla S, Kirkland JL, Lebrasseur NK, Miller JD, Passos JF, Pignolo RJ, Tchkonia T, Niedernhofer LJ (2021) Senolytic drugs: reducing senescent cell viability to extend health span. Annu Rev Pharmacol Toxicol 61:779–803
Rodrigues LP, Teixeira VR, Alencar-Silva T, Simonassi-Paiva B, Pereira RW, Pogue R, Carvalho JL (2021) Hallmarks of aging and immunosenescence: connecting the dots. Cytokine Growth Factor Rev 59:9–21
Romashkan S, Chang H, Hadley EC (2021) National institute on aging workshop repurposing drugs or dietary supplements for their senolytic or senomorphic effects: considerations for clinical trials. J Gerontol A Biol Sci Med Sci. 76:1144–1152
Rosas-Gonzalez VC, Tellez-Banuelos MC, Hernandez-Flores G, Bravo-Cuellar A, Aguilar-Lemarroy A, Jave-Suarez LF, Haramati J, Solorzano-Ibarra F, Ortiz-Lazareno PC (2020) Differential effects of alliin and allicin on apoptosis and senescence in luminal A and triple-negative breast cancer: Caspase, DeltaPsim, and pro-apoptotic gene involvement. Fundam Clin Pharmacol 34:671–686
Russo GL, Spagnuolo C, Russo M, Tedesco I, Moccia S, Cervellera C (2020) Mechanisms of aging and potential role of selected polyphenols in extending healthspan. Biochem Pharmacol 173:113719
Saccon TD, Nagpal R, Yadav H, Cavalcante MB, Nunes ADC, Schneider A, Gesing A, Hughes B, Yousefzadeh M, Tchkonia T, Kirkland JL, Niedernhofer LJ, Robbins PD, Masternak MM (2021) Senolytic combination of Dasatinib and Quercetin alleviates intestinal senescence and inflammation and modulates the gut microbiome in aged mice. J Gerontol A Biol Sci Med Sci, glab002. https://doi.org/10.1093/gerona/glab002. Online ahead of print
Salehi B, Venditti A, Sharifi-Rad M, Kregiel D, Sharifi-Rad J, Durazzo A, Lucarini M, Santini A, Souto EB, Novellino E, Antolak H, Azzini E, Setzer WN, Martins N (2019) The therapeutic potential of apigenin. Int J Mol Sci 20:1305
Salekeen R, Barua J, Shaha PR, Islam KMD, Islam ME, Billah MM, Rahman SMM (2021) Marine phycocompound screening reveals a potential source of novel senotherapeutics. J Biomol Struct Dyn 1–15. https://doi.org/10.1080/07391102.2021.1877822. Online ahead of print
Santoro A, Martucci M, Conte M, Capri M, Franceschi C, Salvioli S (2020) Inflammaging, hormesis and the rationale for anti-aging strategies. Ageing Res Rev 64:101142
Schafer MJ, Zhang X, Kumar A, Atkinson EJ, Zhu Y, Jachim S, Mazula DL, Brown AK, Berning M, Aversa Z, Kotajarvi B, Bruce CJ, Greason KL, Suri RM, Tracy RP, Cummings SR, White TA, Lebrasseur NK (2020) The senescence-associated secretome as an indicator of age and medical risk. JCI Insight 5:e133668
Selvarani R, Mohammed S, Richardson A (2020) Effect of rapamycin on aging and age-related diseases-past and future. Geroscience 43:1135–1158
Seto B (2012) Rapamycin and mTOR: a serendipitous discovery and implications for breast cancer. Clin Transl Med 1:29
Sharifi-Rad J, Rayess YE, Rizk AA, Sadaka C, Zgheib R, Zam W, Sestito S, Rapposelli S, Neffe-Skocinska K, Zielinska D, Salehi B, Setzer WN, Dosoky NS, Taheri Y, el Beyrouthy M, Martorell M, Ostrander EA, Suleria HAR, Cho WC, Maroyi A, Martins N (2020) Turmeric and its major compound curcumin on health: bioactive effects and safety profiles for food, pharmaceutical, biotechnological and medicinal applications . Front Pharmacol 11:01021

Sharma R, Padwad Y (2020) Nutraceuticals-based immunotherapeutic concepts and opportunities for the mitigation of cellular senescence and aging: a narrative review. Ageing Res Rev 63:101141

Shen CY, Jiang JG, Yang L, Wang DW, Zhu W (2017) Anti-ageing active ingredients from herbs and nutraceuticals used in traditional Chinese medicine: pharmacological mechanisms and implications for drug discovery. Br J Pharmacol 174:1395–1425

Short S, Fielder E, Miwa S, von Zglinicki T (2019) Senolytics and senostatics as adjuvant tumour therapy. EBioMedicine 41:683–692

Song P, Zhao Q, Zou MH (2020) Targeting senescent cells to attenuate cardiovascular disease progression. Ageing Res Rev 60:101072

Taetzsch A, Roberts SB, Bukhari A, Lichtenstein AH, Gilhooly CH, Martin E, Krauss AJ, Hatch-Mcchesney A, Das SK (2021) Eating timing: associations with dietary intake and metabolic health. J Acad Nutr Diet 121:738–748

Tavella T, Rampelli S, Guidarelli G, Bazzocchi A, Gasperini C, Pujos-Guillot E, Comte B, Barone M, Biagi E, Candela M, Nicoletti C, Kadi F, Battista G, Salvioli S, O'Toole PW, Franceschi C, Brigidi P, Turroni S, Santoro A (2021) Elevated gut microbiome abundance of Christensenellaceae, Porphyromonadaceae and Rikenellaceae is associated with reduced visceral adipose tissue and healthier metabolic profile in Italian elderly. Gut Microbes 13:1–19

Thompson PJ, Shah A, Ntranos V, Van Gool F, Atkinson M, Bhushan A (2019) Targeted elimination of senescent beta cells prevents type 1 diabetes. Cell Metab 29(5):1045–1060.e10

Triana-Martinez F, Picallos-Rabina P, Da Silva-Alvarez S, Pietrocola F, Llanos S, Rodilla V, Soprano E, Pedrosa P, Ferreiros A, Barradas M, Hernandez-Gonzalez F, Lalinde M, Prats N, Bernado C, Gonzalez P, Gomez M, Ikonomopoulou MP, Fernandez-Marcos PJ, Garcia-Caballero T, del Pino P, Arribas J, Vidal A, Gonzalez-Barcia M, Serrano M, Loza MI, Dominguez E, Collado M (2019) Identification and characterization of Cardiac Glycosides as senolytic compounds. Nat Commun 10:4731

Vaiserman A, Koliada A, Lushchak O, Castillo MJ (2021) Repurposing drugs to fight aging: the difficult path from bench to bedside. Med Res Rev 41:1676–1700

Viana SD, Reis F, Alves R (2018) Therapeutic use of mTOR inhibitors in renal diseases: advances, drawbacks, and challenges. Oxid Med Cell Longev 2018:3693625

Wang J, Wong YK, Liao F (2018) What has traditional Chinese medicine delivered for modern medicine? Expert Rev Mol Med 20:e4

Wang S, Zhang S, Wang S, Gao P, Dai L (2020) A comprehensive review on Pueraria: Insights on its chemistry and medicinal value. Biomed Pharmacother 131:110734

Wang Y, Chang J, Liu X, Zhang X, Zhang S, Zhang X, Zhou D, Zheng G (2016) Discovery of piperlongumine as a potential novel lead for the development of senolytic agents. Aging (Albany NY) 8:2915–2926

Wang Z, Zeng M, Wang Z, Qin F, Chen J, He Z (2021) Dietary Luteolin: a narrative review focusing on its pharmacokinetic properties and effects on glycolipid metabolism. J Agric Food Chem 69:1441–1454

Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, Inman CL, Ogrodnik MB, Hachfeld CM, Fraser DG, Onken JL, Johnson KO, Verzosa GC, Langhi LGP, Weigl M, Giorgadze N, Lebrasseur NK, Miller JD, Jurk D, Singh RJ, Allison DB, Ejima K, Hubbard GB, Ikeno Y, Cubro H, Garovic VD, Hou X, Weroha SJ, Robbins PD, Niedernhofer LJ, Khosla S, Tchkonia T, Kirkland JL (2018) Senolytics improve physical function and increase lifespan in old age. Nat Med 24:1246–1256

Xu M, Tchkonia T, Ding H, Ogrodnik M, Lubbers ER, Pirtskhalava T, White TA, Johnson KO, Stout MB, Mezera V, Giorgadze N, Jensen MD, Lebrasseur NK, Kirkland JL (2015) JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. Proc Natl Acad Sci U S A 112:E6301–E6310

Yadav V, Krishnan A, Vohora D (2020) A systematic review on Piper longum L.: bridging traditional knowledge and pharmacological evidence for future translational research. J Ethnopharmacol 247:112255

Yang SC, Chen PJ, Chang SH, Weng YT, Chang FR, Chang KY, Chen CY, Kao TI, Hwang TL (2018) Luteolin attenuates neutrophilic oxidative stress and inflammatory arthritis by inhibiting Raf1 activity. Biochem Pharmacol 154:384–396

Yosef R, Pilpel N, Tokarsky-Amiel R, Biran A, Ovadya Y, Cohen S, Vadai E, Dassa L, Shahar E, Condiotti R, Ben-Porath I, Krizhanovsky V (2016) Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. Nat Commun 7:11190

Yoshida S, Nakagami H, Hayashi H, Ikeda Y, Sun J, Tenma A, Tomioka H, Kawano T, Shimamura M, Morishita R, Rakugi H (2020) The CD153 vaccine is a senotherapeutic option for preventing the accumulation of senescent T cells in mice. Nat Commun 11:2482

Yousefzadeh MJ, Zhu Y, McGowan SJ, Angelini L, Fuhrmann-Stroissnigg H, Xu M, Ling YY, Melos KI, Pirtskhalava T, Inman CL, McGuckian C, Wade EA, Kato JI, Grassi D, Wentworth M, Burd CE, Arriaga EA, Ladiges WL, Tchkonia T, Kirkland JL, Robbins PD, Niedernhofer LJ (2018) Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine 36:18–28

Yuan H, Li Y, Ling F, Guan Y, Zhang D, Zhu Q, Liu J, Wu Y, Niu Y (2020) The phytochemical epigallocatechin gallate prolongs the lifespan by improving lipid metabolism, reducing inflammation and oxidative stress in high-fat diet-fed obese rats. Aging Cell 19:e13199

Yuanfeng W, Chengzhi L, Ligen Z, Juan S, Xinjie S, Yao Z, Jianwei M (2021) Approaches for enhancing the stability and formation of sulforaphane. Food Chem 345:128771

Zhang X, Zhang S, Liu X, Wang Y, Chang J, Zhang X, Mackintosh SG, Tackett AJ, He Y, Lv D, Laberge RM, Campisi J, Wang J, Zheng G, Zhou D (2018) Oxidation resistance 1 is a novel senolytic target. Aging Cell 17:e12780

Zhang YJ, Duan Y, Zheng XF (2011) Targeting the mTOR kinase domain: the second generation of mTOR inhibitors. Drug Discov Today 16:325–331

Zheng J, Lu B, Xu B (2021) An update on the health benefits promoted by edible flowers and involved mechanisms. Food Chem 340:127940

Zhu Y, Doornebal EJ, Pirtskhalava T, Giorgadze N, Wentworth M, Fuhrmann-Stroissnigg H, Niedernhofer LJ, Robbins PD, Tchkonia T, Kirkland JL (2017) New agents that target senescent cells: the flavone, fisetin, and the BCL-XL inhibitors, A1331852 and A1155463. Aging (Albany NY) 9:955–963

Zhu Y, Tchkonia T, Fuhrmann-Stroissnigg H, Dai HM, Ling YY, Stout MB, Pirtskhalava T, Giorgadze N, Johnson KO, Giles CB, Wren JD, Niedernhofer LJ, Robbins PD, Kirkland JL (2016) Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. Aging Cell 15:428–435

Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, Palmer AK, Ikeno Y, Hubbard GB, Lenburg M, O'Hara SP, Larusso NF, Miller JD, Roos CM, Verzosa GC, Lebrasseur NK, Wren JD, Farr JN, Khosla S, Stout MB, McGowan SJ, Fuhrmann-Stroissnigg H, Gurkar AU, Zhao J, Colangelo D, Dorronsoro A, Ling YY, Barghouthy AS, Navarro DC, Sano T, Robbins PD, Niedernhofer LJ, Kirkland JL (2015) The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell 14:644–658

Zia A, Farkhondeh T, Pourbagher-Shahri AM, Samarghandian S (2021) The role of curcumin in aging and senescence: molecular mechanisms. Biomed Pharmacother 134:111119