Anti-senescence compounds: a potential nutraceutical approach to healthy aging

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Abstract

The desire of eternal youth seems to be as old as mankind. However, the increasing life expectancy experienced by populations in developed countries also involves a significantly increased incidence of the most common age-related diseases (ARDs). Senescent cells (SCs) have been identified as culprits of organismal aging. Their number rises with age and their senescence-associated secretory phenotype fuels the chronic, pro-inflammatory systemic state (inflammaging) that characterizes aging, impairing the regenerative ability of stem cells and increasing the risk of developing ARDs. A variegated class of molecules, including synthetic senolytic compounds and natural compounds contained in food, have been suggested to possess anti-senescence activity. Senolytics are attracting growing interest, and their safety and reliability as anti-senescence drugs are being assessed in human clinical trials. Notably, since SCs spread inflammation at the systemic level through pro-oxidant and pro-inflammatory signals, foods rich in polyphenols, which exert antioxidant and anti-inflammatory actions, have the potential to be harnessed as "anti-senescence foods" in a nutraceutical approach to healthier aging. We discuss the beneficial effects of polyphenol-rich foods in relation to the Mediterranean diet and the dietary habits of long-lived individuals, and examine their ability to modulate bacterial genera in the gut.

Keywords: cellular senescence, aging, senolytic, polyphenols, anti-senescence diet

Introduction

Aging is the result of a continuous interaction between individuals' genetic makeup and environmental factors, characterized by lifelong damage accumulation and progressive loss of tissue and organ functionality **(Kirkwood, 2017**). Increasingly favorable living conditions – including the availability of food and medical treatment –have been contributing to extend life expectancy in developed countries, raising the proportion of elderly and old individuals in the population **(Menotti et al., 2014**). However, aging involves a rising risk of developing a number of neurodegenerative disorders, cardiovascular disease, diabetes, osteoarthritis, and cancer, which are commonly referred to as age-related diseases (ARDs) (**St Sauver et al., 2015**). Notably, a dramatic increase was also observed in the prevalence of multiple chronic diseases and comorbid health conditions, *i.e.* hypertension and frailty, especially in elderly subjects. The high incidence of disability and comorbidity associated with aging has prompted investigations into how the trajectory of aging can be intercepted to prevent or delay ARD development. Most of the research work performed to date has focused on interventions against the common ARD risk factors, such as hypertension and high glucose, cholesterol, and triglyceride levels. However, mounting evidence suggests that the most effective strategy would be to target the molecular mechanisms shared by all ARDs, rather than try to prevent the separate disorders from arising (**Seals and Melov, 2014; Blagosklonny, 2009)**. Clearly, this requires unraveling the molecular mechanisms that promote aging itself **(Fontana et al., 2015).**

A large body of data indicates that the burden of senescent cells (SCs) accumulating in aging organisms can contribute to spread inflammaging (**Franceschi et al., 2000; Franceschi, 2017)**, pointing at SCs as druggable targets for ARD prevention or treatment **(Sikora et al. 2014; Childs et al., 2015, 2017; Prattichizzo et al., 2016**).

A number of natural and synthetic compounds have been investigated for their anti-senescence and anti-aging potential in cellular and animal models as well as in humans (**Vaiserman et al., 2016;**

Janubová and Žitňanová, 2017). We review the advantages and disadvantages of using medications or natural compounds to counteract or delay senescence and aging and highlight that the safety and efficacy of most potential anti-senescence or senolytic compounds, especially synthetic drugs, are still far from being clearly understood.

Polyphenols (PPs) are natural compounds with documented antioxidant and anti-inflammatory properties that could be harnessed to counteract the signaling through which SCs spread inflammation at the systemic level. Accordingly, PP-rich foods could have "anti-senescence" effects. To substantiate this hypothesis, we analyze and discuss their beneficial effects exerted in the framework of the Mediterranean diet and of the dietary habits of long-lived individuals. Moreover, to assess the mechanisms involved in the putative pro-longevity properties of PP-rich foods, we discuss the interaction of PPs with the gut microbiota in animal models and in humans. Finally, we provide information on some of the best known dietary PPs, with a view to stimulating the consumption of PP-rich foods not only by ARD patients, but also by healthy aging individuals **(Neveu et al., 2010**). This information was obtained from Phenol-Explorer, a database collecting data on natural phenols and PPs found in food, on their processing, and on the PP metabolites investigated in humans and in experimental animals. Vitamins are not addressed in this review.

1. Cellular senescence

1.1 Phenotypes and signaling pathways

In vitro studies have demonstrated that cellular senescence can occur as a consequence of replicative and non-replicative stress (**He and Sharpless, 2017**). Investigation of replicative senescence in cell models has shown that it is associated with limited proliferative capacity in cultured human cells **(Cristofalo et al., 2004)**. Non-replicative senescence can be induced by a variety of stressors – including chemical and physical insults like x-ray exposure, oxidative stress, DNA and chromatin damage, and mitochondrial dysfunction – as well as endogenous processes like transcriptional

stress, *i.e.* overexpression of activated oncogenes **(Coppé et al., 2010**; **Childs et al., 2015)**; the latter has been defined as stress-induced premature senescence (SIPS) (**Toussaint et al., 2000)**.

SCs exhibit distinctive morphological features, such as an enlarged, flattened and irregular morphology, a larger nucleus, a single and larger nucleolus, and an increased number of cytoplasmic vacuoles **(Campisi and d'Adda di Fagagna, 2007)**.

The senescence phenotype is characterized by increased activity of senescence-associated (SA) β-galactosidase (β-gal), a typical lysosomal enzyme. SA β-gal activity (measured at pH 6.0) is frequently employed as a marker of SCs both *in vitro* and *in vivo* (**Dimri et al., 1995)**, although according to some researchers it should be combined with other markers, like p16 **(Severino et al., 2000, Hall et al., 2016)**. The main pathways involved in the acquisition of a senescent phenotype have been explored by transcriptomic and pharmacological approaches (**Shaohua et al., 2015)**. SCs are characterized primarily by the loss of proliferation ability. Cell cycle arrest has long been considered as a potent anticancer mechanism preventing premalignant cell expansion (**Baker et al., 2017**). However, senescence features are expressed in premalignant tumors, where progression to malignancy requires evading senescence (**Burd et al., 2013; Collado and Serrano, 2010**; **Campisi and d'Adda di Fagagna, 2007**). Recent evidence points at a tumor- and relapse-promoting role for senescence in both cell-autonomous and non-cell autonomous mechanisms **(Demaria et al., 2017; Milanovic et al., 2018)**. The suppression of cell cycle progression in SCs is mediated by the overexpression of inhibitory proteins such as p53, p21, and $p16^{InK4a}$ and by the downregulation of proteins stimulating cell replication, like cyclins, c-Fos, and pCNA (**Narita et al., 2003**). Therefore, p16 and p21 are extensively investigated senescence-associated biomarkers.

Besides replicative arrest, SCs undergo a number of other changes involving DNA, mitochondrial function, oxidative balance, lipid and glucose metabolism, and inflammatory signaling.

The main senescence-associated DNA markers – SDF (senescence-associated DNA damage foci) and SAHF (senescence-associated heterochromatin foci) – are commonly detected in SCs as are some markers of DNA damage (*i.e.* p-γH2AX and TAF) **(Noren Hooten and Evans, 2017)**.

Mitochondrial dysfunction and the resulting oxidative metabolism imbalance have been implicated in the development of cellular senescence **(Ziegler et al., 2015; Correia-Melo and Passos, 2015; Correia-Melo et al., 2016)**. Reactive oxygen species (ROS) are emerging as key signaling molecules responsible for spreading senescence from SCs to neighboring cells **(Davalli et al., 2016**). Mitochondrial dysfunction also seems to contribute to the impaired fatty acid metabolism seen in SCs, which is related to the development of age- and diabetes-dependent hepatic steatosis (**Ogrodnik et al., nat comm. 2017**). Senescence therefore induces extensive metabolic and bioenergetic changes (**Quijano et al., 2012)** and SC metabolism has recently been proposed as a target to modulate aging **(Wiley and Campisi, 2016**; **Prattichizzo et al., 2017**).

Two further characteristic features of SCs are an increased but inefficient glycolysis, in association with ATP depletion and AMP accumulation, which in turn can promote cell cycle arrest through AMPK activation (**Zwerschke et al., 2003**). AMPK stimulates ATP production and reduces its consumption, increasing glycolysis and fatty acid oxidation, halting cell growth, biosynthesis, and proliferation, and partially suppressing the mammalian target of rapamycin (mTOR), a nutrient-sensing serine/threonine protein kinase (**Vaiserman et al., 2016; Johnson et al., 2015)**. mTOR is found in cells as two different complexes, complex 1 (mTORC1) and complex 2 (mTORC2) (**Laplante and Sabatini, 2012**); the former is involved in the response to nutrient signaling and in the induction of cell growth and protein synthesis, and reduces autophagy, whereas the latter has a role in the arrangement of the cytoskeleton **(Shaohua et al., 2014**). mTOR activity is increased in SCs, playing a pivotal role in a variety of processes like cell cycle arrest, metabolism, lysosome-autophagy proteolytic system, and secretion of pro-inflammatory factors (**Laberge et al., 2015; Herranz et al., 2015; Moreno-Blas et al., 2018).** Similar to the hypothesis that has been advanced for immune cells, the mTOR network is emerging as a biological mechanism that adjusts the environmental nutritional status to SC activities and fine-tunes the inflammatory response (**Weichhart et al., 2015**). Notably, mTOR is a key modulator of aging in organisms as

evolutionarily divergent as yeasts and rodents, and it is conceivable that this function is to some extent conserved also in humans **(Johnson et al., 2013)**.

Increasing data support a role for silent information regulators (SIRTs/sirtuins), a class of nutrient-sensitive epigenetic regulators, in promoting mammalian health, modulating cellular senescence and lifespan. SIRT1 is a (NAD+) - dependent deacetylase that targets a number of transcription factors such as FOXO1, 3 and 4, p53, NF-κB, PGC-1 and HSF-1, modulating in turn a number of cellular stress adaptive responses **(Hwang et al., 2013).** SIRT1 can deacetylates p53 in a NAD+-dependent manner to inhibit p53 transcription, modulating pathways involved in cellular and organismal aging **(Ong and Ramasami, 2018).** Importantly, Sirtuins are themselves regulated by diet and environmental stress **(Imai and Guarente, 2014)**.

Despite the large body of information that has become available on a number of cellular senescence inducers and on the main metabolic pathways involved in its development and maintenance, the clinical relevance of SCs *in vivo* is still far from clear. Due to complex and not stereotypical nature of senescence (**Childs et al 2016; Hall et al 2016**), a combination of markers is required to identify SCs *in vivo* (**Childs et al., 2016**). However, new and practical technologies are now available to quantify the senescence burden in *ex vivo* samples (**Biran et al., 2017 Aging cell).**

1.2 The SASP

Although the irreversible cell cycle arrest is commonly considered as the key characteristic of SCs, another major feature is the acquisition of a senescence-associated secretory phenotype (SASP), which is characterized by a powerful pro-inflammatory action (**Coppé et al., 2010**). Experimental data strongly suggest that SASP acquisition by SCs participates in microenvironment modulation. SCs secrete a large number of factors, which differ in relation to the cell type and stressor involved. The SASP involves secretion of hundreds of molecules, of which interleukin (IL)-1 α/β, IL-6, IL-8, transforming growth factor (TGF)-β, and tumor necrosis factor (TNF)-α are the best characterized (**Coppè et al., 2010; Childs et al., 2015; Prattichizzo et al., 2016a)**. Some of these

cytokines/chemokines can induce or reinforce the senescent phenotype by acting in an autocrine and paracrine manner, spreading senescence *via* a "bystander effect" (**Acosta et al., 2013)**. In particular, membrane-bound IL-1α is an upstream master regulator of the SASP, IL-1β and TGF-β mediate senescence spread, and the downstream products IL-6 and IL-8 reinforce autocrine senescence (**Campisi PNAS 2009; Acosta et al., 2013; Kuilman Cell 2008; Prattichizzo et al 2016 b**). The SASP is mostly induced by NF-kB, the master transcription factor of the immune system. Upstream, Janus kinase (JAK), p38, and other MAP kinases have all been implicated in SASP control, whereas activation of the NLRP3 inflammasome mediates paracrine senescence (**Childs et al., 2015; Andriani et al., 2016; Ferrand et al., 2015; Acosta et al., 2013**).

Epigenetic modifiers, *i.e.* non-coding RNAs, have also been reported to play a role in the SASP and its systemic spread (**Olivieri et al., 2015**); moreover, complex epigenetic mechanisms seem to modulate the pathways involved in SASP acquisition (**Hekmatimoghaddam et al., 2017)**. There is strong evidence that SIRTs, can modulate SASP and senescence, extending lifespan/health-span, in different animal models **(Hayakawa et al., 2015; Kida et al., 2016; Wiley et al., 2016)**.

The release of SASP factors, including proteins and nucleic acids, at the paracrine and systemic level fuels inflammation and induces the recruitment of immune cells, to clear damaged cells from tissues **(Lunyak et al., 2017)**. Therefore, senescence seems to have evolved as a protective mechanism against damage induced by a variety of stressors and to play a physiological role in promoting wound healing, reducing transformed cell expansion, limiting fibrosis, and helping embryo development and cellular reprogramming *in vivo* **(Krizhanovsky et al., 2008; Muñoz-Espín et al., 2013; Demaria et al., 2014; Mosteiro et al., 2016)**. However, a chronic SASP is associated with senescence spread, a heightened pro-inflammatory status, and a faster aging rate **(Acosta et al., 2013; Baker et al., 2016)**. In the framework of the aging process, excessive SC accumulation and systemic SASP spread have thus turned a protective response into a pathogenic mechanism.

In vivo studies have demonstrated that a number of SASP-associated factors are overexpressed in all aged organisms analyzed (**Starr et al., 2014; Arai et al., 2015; Adriaensen et al., 2015)**. These factors are also involved in ARD development and progression (**He and Sharpless, 2017**). Indeed, overexpression of SASP-related molecules has been described in type 2 diabetes mellitus (T2DM) (**Prattichizzo et al., 2016b; 2017**), osteoarthritis **(Martin et al., 2004)**, atherosclerosis (**Zhou et al., 2006**), chronic obstructive pulmonary disease (COPD) (**Yanagi et al., 2017**), glaucoma **(Liton et al., 2005)**, and cancer (**Lecot et al., 2016; Milanovic et al., 2018)**.

The demonstration that SC clearance is sufficient to delay ARD development and extend lifespan in mice has prompted intense research into the pathways leading to SC build-up and the molecular mechanism governing the SASP, with a view to developing new therapeutic strategies to eliminate SCs and/or attenuate the systemic and local effects of the SASP (**Baker et al., 2016; Kirkland et al., 2017)**. Work on the effects of newly designed or repurposed drugs tailored to prevent SC accumulation, restrain their secretory activity, achieve their selective elimination, and reduce possible off-target effects is in progress (**Kirkland and Tchkonia, 2011; Kirkland et al., 2017**).

2. Synthetic anti-senescence compounds

A key objective of current gerontology research is to develop drugs capable of modulating the aging process. The goal of promoting healthy aging can be achieved by at least two molecular mechanisms: SASP suppression and/or SC clearance using senolytic compounds. Since the SASP exerts a powerful pro-oxidant and pro-inflammatory action on the microenvironment, it is likely that molecules with antioxidant or anti-inflammatory properties can serve as anti-SASP agents.

The compounds with anti-aging or anti-SASP properties can be divided into those that are fully synthesized (because they are not found in nature), semi-synthesized (*via* chemical modification of substances from micro-organisms or plants), or completely natural. Although some synthetic molecules developed to treat a variety of conditions, *i.e.* chemotherapeutics, can modulate SASP acquisition, they may also induce significant adverse effects. As a result, their clinical development

will be limited to conditions where they have a favorable benefit/risk ratio. This is the case of some synthetic drugs with senolytic activity. Since senolytic research is still in its infancy, translation of preclinical data to human trials will require the identification of human parameters as well as of measurable markers and outcomes (**Hastings et al., 2017; Matjusaitis et al., 2017).**

The anti-senescence effect of molecules with senolytic action – such as dasatinib, Bcl family inhibitors, panobinostat, HSP90 inhibitors, forkhead box proteins O (FOXO) targeting peptide, and 2-deoxy-D-glucose – and molecules with SASP-suppressing activity – like metformin (a hypoglycemic drug), rapamycin (a specific mTOR pathway inhibitor), and JAK inhibitors – is detailed below.

2.1 Synthetic compounds with senolytic properties

Dasatinib

Dasatinib, an oral tyrosine kinase inhibitor, is an anticancer drug that inhibits the ability of cells to duplicate and migrate, inducing apoptosis **(Montero et al., 2011)**. It was approved by the FDA for first line use in patients with chronic myelogenous leukemia. Its most common adverse effects include hematological toxicity and gastrointestinal and respiratory side effects (**Hartmann et al., 2009; Suresh et al., 2017**). According to a recent study dasatinib eliminated SCs with an efficacy that was cell type-dependent **(Zhu et al., 2015)**. Interestingly, dasatinib combined with quercetin (a flavonol) cleared senescent preadipocytes, endothelial cells, and primary mouse embryonic fibroblasts (MEFs) more effectively than used alone (**Zhu et al., 2015)**. This study provided the first evidence that mouse healthspan could be extended with senolytic compounds, as shown by improvements in the aging score of progeroid mice and of cardiac function in naturally aged mice. These findings demonstrate the efficacy of senolytics in delaying aging-associated symptoms of frailty and in extending healthspan.

Navitoclax and other Bcl family inhibitors

Navitoclax (previously ABT-263) is an anticancer drug and the senolytic compound investigated most extensively in animal models. It is a potent activator of the mitochondrial apoptotic pathway, inhibiting Bcl family members such as Bcl-2, Bcl-xl and Bcl-w protein and promoting the release of proapoptotic factors like Bim (**Tse et al., 2008**). Its most common adverse effects are gastrointestinal; fatigue is relatively frequent but not dose-limiting. Thrombocytopenia is due Bcl-xl inhibition, which results in reduced platelet lifespan (**Wyndhamet al., 2010; Gandhi et al., 2011; Xiong et al., 2014)**. *In vitro* studies have highlighted a cell type-dependent senolytic effect. Navitoclax adversely affects the viability of various SC types such as human lung fibroblasts (IMR-90), human umbilical vein endothelial cells (HUVECs), and MEFs, but not of human senescent primary preadipocytes (**Zhu et al., 2016**). Accordingly, short interfering RNA targeting Bcl-xl exerted a senolytic action on HUVECs but not on preadipocytes **(Zhu et al., 2016)**. Navitoclax administered to sub-lethally irradiated mice markedly reduced the number of senescent muscle stem cells and senescent bone marrow hematopoietic stem cells, whereas in normally aged mice it induced rejuvenation of aged muscle tissue and of the hematopoietic compartment (**Chang et al., 2016**). In addition, it efficiently cleared senescent macrophages in atherosclerosis-prone low-density lipoprotein receptor-deficient mice, reducing microenvironmental inflammation in the arterial wall and stabilizing atherosclerotic plaques (**Childs et al., 2016)**. Finally, navitoclax promoted the clearance of SCs arising after treatment with cytotoxic chemotherapeutics, *i.e.* doxorubicin, thus mitigating the harmful effects of the SASP on cancer relapse and metastasis (**Demaria et al., 2017).** Other drugs of the same family may have senolytic activity. ABT-737 specifically induces SC apoptosis due to joint inhibition of Bcl-w and Bcl-xl. In mice, it efficiently removed SCs induced by DNA damage in the lung and SCs induced by p53 activation through transgenic p14(ARF) in the epidermis **(Yosef et al., 2016)**; the increased proliferation of hair follicle stem cell seen after SC elimination from the epidermis strongly suggests that SC clearance could enhance tissue regeneration ability.

Panobinostat

This anticancer drug was approved by the FDA in 2015 to treat multiple myeloma **(Yoon et al., 2016)**. Combined with the anticancer agent bortezomib and corticoid dexamethasone, it is generally well tolerated by adult patients; its most common side effects are hematological and gastrointestinal **(San-Miguel et al., 2014)**. There is recent evidence of its senolytic activity on senescent non-small cell lung cancer and head and neck squamous cell carcinoma. Cytotoxic treatment with cisplatin or taxol was associated with a consistent pro-senescence response in the cell population surviving the insult. Panobinostat administered alone selectively killed SCs, thereby proving an effective post-chemotherapy senolytic **(Samaraweera et al., 2017).**

HSP90 inhibitors

Heat shock protein 90 (HSP90) inhibitors have recently been suggested as promising senolytic drugs (**Fuhrmann-Stroissnigg et al., 2017**). Among 97 drugs screened *in vitro*, two HSP90 inhibitors were found to possess senolytic activity: geldanamycin and its derivative 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG) **(Trepel et al., 2010)**. Importantly, repeated intermittent courses of 17-DMAG significantly delayed the onset of multiple age-related symptoms in progeroid mice, leading to an overall healthspan improvement associated with a 50% reduction in p16INK4a expression in the kidney (**Fuhrmann-Stroissnigg et al., 2017**). It has been stressed that despite their poor water solubility and high toxicity, other HSP90 inhibitors could be tested in clinical trials for their chemotherapeutic ability, either alone or as drug sensitizers in combination with other drugs or with irradiation **(Sidera et al., 2014).**

FOXO4-p53 targeting peptide

FOXO are a class of transcription factors, activated downstream of IGF-1, that have been associated with the aging process **(Neumann-Haefelin et al., 2008)**. The finding that FOXO4 plays a central role in SC viability has recently led to the design of a FOXO4 peptide modified to form a D-retro inverso (DRI) isoform directed at perturbing FOXO4 - p53 interaction (**Baar et al., 2017)**. In this study, treatment selectively caused p53 nuclear exclusion and cell-intrinsic apoptosis in SCs; moreover, treatment of fast-aging XpdTTD/TTD mice and naturally aged mice restored fitness, fur

density, and renal function, extending healthspan and also ameliorating doxorubicin-induced chemotoxicity. Even though FOXO4 peptide was well tolerated at doses that can have senolytic effects, no safety data are available in humans.

2-Deoxy-D-glucose

Increased glucose consumption by SCs enhances survival, paralleling a phenomenon that is seen in cancer cells **(Wiley et al., 2016)**. 2-deoxy-D-glucose (2-DG) is a glucose molecule where substitution of the 2-hydroxyl group with hydrogen induces toxicity **(Raez et al., 2013; Dörr et al., 2013)**. A phase I trial has been set up to evaluate the safety, pharmacokinetics, and maximum tolerated dose of 2-DG combined with docetaxel in patients with advanced solid tumors **(Raez et al., 2013)**. Recently, 2-DG has successfully been used *in vitro* to achieve selective removal of senescent vascular smooth muscle cells and *in vivo* to clear SCs in a tumor model of treatment-induced senescence **(Gardner et al., 2015; Dörr et al., 2013).**

2.2 Synthetic compounds with anti-SASP properties

Metformin

Metformin is a biguanide originally introduced in clinical practice as an oral hypoglycemic drug for the first line treatment of T2DM **(American Diabetes Association, 2017; Garber et al., 2017**). Its therapeutic role is expanding to include treatment of pre-diabetes, gestational diabetes, polycystic ovarian disease, and treatment or prevention of pre-eclampsia **(Lord et al., 2003)**. Metformin reduces intestinal glucose absorption and liver glucose production and heightens insulin sensitivity by increasing peripheral glucose uptake and utilization (**Dumitrescu et al., 2015**). It activates a variety of molecular mechanisms: AMPK in the liver, which improves insulin signaling, whole body energy balance, and glucose and lipid metabolism (**Towler et al., 2007)**; inhibition of glucagon-induced cAMP elevation with reduced activation of protein kinase A (PKA); inhibition of mitochondrial glycerophosphate dehydrogenase and of the mitochondrial respiratory chain (complex I); and effects on the gut microbiota (**Rena et al., 2017)**. Metformin is generally well

tolerated (**Triggle et al., 2017**). Its most common adverse effects are gastrointestinal **(Okayasu et al., 2012)**. A rare but severe complication is lactic acidosis **(Lipska et al., 2011)**.

Metformin affects a number of aging-associated pathways such as inflammation, autophagy, cell survival, and protein synthesis. It modulates the expression of receptors for cytokines, insulin, and IGF-1, it activates intracellular AMPK and enhances mTOR inhibition (**Barzilai et al., 2012**). Metformin treatment increased lifespan and prevented cancer in *Caenorhabditis elegans* (**Onken et al., 2010**) as well as in rodents (**Anisimov et al., 2011**). Metformin induced lowering of p16 and p21 protein, reduced the abundance of inflammatory cytokines, and reduced oncogene expression in several senescence models, like fibroblasts *in vitro* and vessels of high fat-fed mice *in vivo* **(Forouzandeh et al., 2014)**. In addition, it has been suggested as an effective SASP-suppressing molecule in senescent fibroblasts (**Moiseeva et al., 2013)**.

A variety of mechanisms have been proposed to explain its anti-senescence and anti-inflammatory activity, including direct or indirect effects on the NF-kB pathway, mTOR activity, ACAD10 expression, and interaction with the gut microbiota (**Barzilai et al., 2016**). Recently, chronic metformin treatment has been reported to upregulate DICER1 in mice as well as humans, increasing the expression of a subset of microRNAs (miR-20a, miR-34a, miR-130a, miR-106b, miR-125, and let-7c) associated with senescence and aging-related pathways **(Noren Hooten et al., 2016**). Metformin treatment may affect gene expression through microRNA (miRNA) modulation. A recent systematic review has reported a significant reduction in all-cause mortality and ARD incidence associated with metformin, suggesting that it may extend lifespan and healthspan also in humans (**Campbell et al., 2017**).

Rapamycin

Rapamycin (sirolimus), a macrolide compound isolated from the bacterium *Streptomyces hygroscopicus* in 1972, exerts a potent immunosuppressive and antiproliferative action on T and B cells by inhibiting IL-2 and other cytokine receptor-dependent signal transduction mechanisms (**Dumont et al., 1996)**. These properties stem from its ability to inhibit mTOR, an evolutionarily

conserved serine/threonine kinase that plays a key role in balancing cell growth and cell death in response to nutritional status, growth factor, and stress signals **(Paquette et al., 2018)**. mTOR also plays a crucial role in regulating autophagy (**Kim and Guan, 2015)**.

Rapamycin is currently used to prevent transplant rejection, to treat lymphangioleiomyomatosis (a rare, progressive lung disease), and to coat coronary stents to prevent restenosis after balloon angioplasty **(Li et al., 2014)**. Its major and most common adverse effects include anemia, thrombocytopenia, peripheral edema, nausea, diarrhea, hypertension, and increased creatinine, triglyceride, and cholesterol levels **(Martinet et al., 2014)**. An uncommon but potentially fatal adverse effect is non-infectious pneumonitis characterized by a non-malignant, non-infectious, and non-specific inflammatory infiltrate combined with negative bacterial tests of blood and bronchoalveolar lavage (**Moes et al., 2015).**

A number of studies in mice and monkeys have demonstrated that rapamycin can extend lifespan and improve age-related functional decline by targeting mTORC1 **(Harrison et al., 2009; Miller et al., 2014; Tardif et al., 2015)**. Its anti-aging effects involve both anti-senescence and SASP-suppressing properties **(Demidenko et al., 2009; Wang et al., 2017**). Mechanistically, rapamycin can raise Nrf2 levels, which are usually diminished in senescent tissue, reducing cell senescence through autophagy activation **(Wang et al., 2017)**. As regards SASP suppression, rapamycin-induced mTOR inhibition reduces IL-1α translation, thus suppressing the main pathways favoring SASP factor secretion (**Laberge et al., 2015**). Notably, *in vivo* administration attenuates the pro-tumorigenic effect of SCs **(Wang et al., 2017)**.

JAK inhibitors

JAK is a family of intracellular tyrosine kinases that transduce cytokine-mediated signals *via* the JAK-STAT (signal transducer and activator of transcription) pathway, a pleiotropic cascade that is involved in the transduction of a multitude of signals with roles in development and homeostasis in organisms spanning from flies to humans (**Aaronson and Horvath. 2002**).

Targeting kinases is a promising strategy in the therapeutic approach to ARDs **(Cano et al., 2017)**. The JAK pathway is more highly active in senescent than non-senescent cells, and its inhibition induces SASP suppression in SCs, reducing age-related dysfunction **(Xu et al., 2015, 2016)**. *In vivo* treatment with JAK inhibitors improves a composite frailty index and enhances insulin sensitivity in old mice **(Xu et al., 2015)**. A number of JAK inhibitors are approved to treat inflammatory diseases like psoriasis and rheumatoid arthritis. Potential adverse effects of their anti-inflammatory action include an increased susceptibility to infections and immune system disorders **(Winthrop et al., 2017)**.

Aspirin

On interesting study showed that aspirin improves lifespan in genetically heterogeneous male mice suggesting that lack of effects of aspirin on life span in females could be related to gender differences in drug disposition or metabolism **(Strong et al., 2008).** Being involved in restrain the production of arachidonic acid metabolites, modulators of inflammation, low-dosage aspirin administration should be repurposed as an anti-SASP agent (**Phillips and Leeuwenburgh, 2004).**

3. Natural anti-senescence compounds

Numerous substances from the natural world can interact with biological processes. They are referred to as bioactive compounds; those contained in food have been named "nutraceuticals" **(Biesalski et al., 2009**). Intense research work is being devoted to identify nutraceuticals that can help prevent pathological conditions, especially ARDs, and/or mimic the anti-aging action exerted by metformin and rapamycin, but without their adverse effects. A number of novel metformin and rapamycin mimics, including allantoin, ginsenoside, and epigallocatechin gallate, have recently emerged as promising candidates for experimental validation (**Aliper et al., 2017)**. The interesting hypothesis that bioactive compounds contained in food may extend healthspan through SASP

modulation points at new strategies to slow down ARD onset and development (**Pazoki-Toroudi et al., 2016**).

Although it has long been known that nutrients affect human health, the molecular mechanisms through which food can influence the health status are still insufficiently known. In this connection it has been reported that several bioactive compounds can act as epigenetic modifiers, modulate gene expression, chromatin assembly status, DNA methylation patterns, and non-coding RNA expression (miRNAs, siRNAs, piRNAs) (**Bacalini et al., 2014; Lee et al., 2017**). A number of studies have suggested that PP–rich foods can modulate the activity of DNA writers/readers such as DNA methyltransferase (DNMT), histone deacetylases (HDACs), histone acetyl transferases (HATs), and HDAC SIRTs, highlighting a new molecular mechanism that may contribute to healthy aging **(Szarc vel Szic et al., 2015**). Accordingly, it may be argued that some compounds can modulate the acquisition and maintenance of the cellular senescence program, which are cell type- and dose-dependent. Notably, the epigenetic profile acquired by cells can be inherited, at least in part, by subsequent cell generations, in a sort of "epigenetic memory" (**Trerotola et al., 2015)**.

Mounting evidence suggests that different classes of phytochemicals are able to modulate the senescence process (**Kuilman et al., 2010**), supporting the value of nutraceutical research to promote healthier aging (**Janubová and Žitňanová et al., 2017**). Information on the anti-aging effects of a number of natural and synthetic compounds is available from Geroprotectors and DrugAge **(http://genomics.senescence.info/drugs/index.php; http://geroprotectors.org/)**.

3.1 Natural compounds with senolytic properties

Since the anti-aging effects of natural compounds have only recently begun to be evaluated scientifically, little evidence is available with regard to their properties and their ability to exert anti-SASP and/or senolytic activity. Yet, whereas ample evidence has been provided for the anti-SASP effects of a number of natural compounds, data on their senolytic activity are still limited. This is not surprising, since the characterization of senolytic properties is itself a novel research

area. Most of the available data regard quercetin, tocopherol, and piperlongumine (PL) **(Khor et al., 2016; Hwang et al., 2018)**, but additional information on natural and synthetic substances is expected in the near future.

Tocotrienols

Tocotrienols, the least known members of the vitamin E family, possess well-established antioxidant properties and play recognized roles in cell signaling, immune response, and apoptosis. Recently, they have emerged as nutrients with senolytic properties. They exert two complementary effects: they stimulate senescence in cancer cells, thus reducing their malignant potential **(Malavolta et al., 2016**) and slow down the aging process by reducing SC accumulation in healthy tissue (**Durani et al., 2015)**.

Quercetin

Tocotrienols can exert their beneficial effects also in combination with quercetin, a flavonol found in several fruits and vegetables; like tocotrienols, quercetin exerts a dual and complementary action: it can induce senescence and promote cell death in aging cells and it can delay senescence and/or promote SC clearance in healthy tissue (**Hwang et al., 2018**). As noted above, a senolytic cocktail of quercetin and dasatinib induced marked effects on healthspan in a variety of mouse models (**Zhu et al 2015; Ogrodnik et al., 2017**). The anti-SASP action of quercetin is examined in the next paragraph.

Piperlongumine

PL is a natural product of *Piper longum*, which has long been known for its anticancer activity **(Golovine et al., 2015**). It inhibits malignant phenotypes by suppressing cancer stemness and can thus serve as an effective anticancer agent **(Chen et al., 2018)**. It has recently been demonstrated that PL preferentially kills senescent human WI-38 fibroblasts when senescence is induced by ionizing radiation, replicative exhaustion, or ectopic expression of the Ras oncogene **(Wang et al., 2016)**.

3.2 Natural compounds with anti-SASP properties

PPs are highly interesting natural compounds with anti-SASP properties. About 10,000 PPs have been identified in the food commonly eaten in developed countries, like fruit, vegetables, tea, wine, and grain cereals **(Li et al., 2014)**. Their concentration is affected by a variety of factors like sun exposure, rainfall, degree of ripeness, processing, storage, and cooking process (**Bouaziz et al., 2004; Gomez-Rico et al., 2006; Ferracane et al., 2008**; **Miglio et al., 2008)**.

PPs are classified based on phenol ring number and the elements they bind, and are grouped into flavonoids and non-flavonoids. The former include six subsets of compounds, flavonols, flavones, flavonones, flavanoles, isoflavones, and anthocyanins, whereas non-flavonoids include phenolic acids, lignans, stilbenes, and tannins. Their fundamental chemical structure usually involves a linkage to one or more sugars, amines, carboxylic and organic acids, lipids, or other phenols (**Kondratyuk et al., 2004**). The main PP classes are listed in **Figure 1, A and B.**

The most extensively documented biological properties of PPs are antioxidant and anti-inflammatory actions (**Yu et al., 2016**; **Gao et al., 2015**). Therefore, since ROS are involved in the pro-inflammatory signaling exploited by SCs to spread inflammation at the systemic level and can be considered as SASP factors (**Zinovkin et al., 2014, Park et al., 2017**; **Nelson et al., 2017**), the anti-ROS and anti-inflammatory activity of PPs may be defined as anti-SASP.

A number of *in vitro* and *in vivo* studies have suggested that PPs can protect cells from inflammation-related damage by modulating the activation of the major pro-inflammatory pathways, such as phospholipase A_2, cyclooxygenase (COX), and NF-kB (**Kim et al., 2004, Stangl et al., 2007; Larrosa et al., 2009**; **Soobrattee et al., 2012)**. Since SCs and the SASP are important contributors to inflammaging, which is considered as the main risk factor for the development of the most common ARDs (**Olivieri et al., 2017**)**,** the anti-senescence effect of PPs could contribute to delay ARD development. Cardio- and neuroprotective functions, like reduction of postprandial hyperlipemia (**Li et al., 2014**) and insulin resistance (**Dasgupta et al., 2007; Meydani and Hasan, 2010**), have been described for a number of PPs (**Sun et al., 2017)**. A reduction in glucose uptake in

tumor cells, induced by a number of PPs, has been suggested as an anticancer effect **(Soga, 2013**) and has been described in several human cancers **(Pandey and Rizvi, 2009; Niedzwiecki et al., 2016**). Since SCs require large amounts of energy to produce SASP factors, interventions aimed at reducing glucose uptake have been proposed to decrease the SC burden (**Malavolta et al., 2014).**

The potential anti-senescence effects of the most extensively investigated PPs contained in food are briefly described below. The foods with the highest concentration of PPs with putative anti-senescence activity are listed **in Table 1.**

Curcumin

Curcumin is a yellow pigment of the *Curcuma longa* (turmeric) plant. It has a number of pharmacological effects, including antioxidant and anti-inflammatory properties **(Argyropoulou et al., 2013**). Curcumin improves the viability of retinal pigment epithelial cells, reducing oxidative stress (**Zhu et al., 2015)**; in animal models like *C. elegans* and *Drosophila* it enhances the antioxidant response transcription factor SKN-1/NRF2, thus countering oxidative stress and lipid peroxidation **(Argyropoulou et al., 2013)**. Curcumin treatment has been seen to modulate epigenetic enzymes such as HDACs (HDAC1, HDAC3, HDAC8), sirtuins (SIRT1) **(Grabowska et al., 2017**), and transcriptional co-activator proteins (p300 histone acetyltransferase), and to increase lifespan in some animal models (**Argyropoulou et al., 2013**). The major obstacles hampering its administration are its hydrophobicity and poor oral bioavailability. However, new strategies such as curcumin-loaded micelles are being explored to improve delivery (**Wang et al., 2017**).

Quercetin, naringenin, apigenin, and kaempferol

The antioxidant properties of quercetin have extensively been documented in *in vitro* cellular models, especially fibroblasts **(Chondrogianni et al., 2010)**. Moreover, a number of PPs such as quercetin, naringenin, apigenin, and kaempferol have been reported to exert anti-SASP effects on human fibroblasts in which senescence was induced with bleomycin (**Lim et al., 2015)**. Besides an ability to enhance oxidative stress resistance, they have been seen to induce a rejuvenating effect on

senescent fibroblasts (**Chondrogianni et al., 2010)** and to extend life expectancy in *in vivo* models like *Saccharomyces cerevisiae* (**Belinha et al., 2007**) and *C. elegans* (**Argyropoulou et al., 2013**).

Epigallocatechin gallate, catechin, and genistein

Anti-senescence effects have also been reported for epigallocatechin gallate, catechin, and genistein **(Argyropoulou et al., 2013)**. Epigallocatechin gallate inhibited H_2O_2-induced senescence in human dermal fibroblasts and reduced the level of acetylated p53 **(Han et al., 2012**). Genistein attenuated stress-induced senescence in HUVECs and human vascular smooth muscle cells by activating AMPK and inhibiting mTOR (**Lee et al., 2016**). It has also been reported to modulate the microbiome in humanized mice; such modulation may enhance its effects on breast tumor, where it increased cancer latency and reduced its growth **(Paul et al., 2017)**.

Resveratrol and pterostilbene

Resveratrol and its derivative pterostilbene possess anti-aging effects *via* modulation of oxidative damage, inflammation, telomere attrition, and cell senescence (**Li et al., 2017)**.

Resveratrol has been demonstrated to prevent/delay senescence in a number of cell models, like human umbilical cord fibroblasts **(Yamashita et al., 2012**) and human mesenchymal stem cells (**Peltz et al., 2012; Mikuła-Pietrasik et al., 2015)**, and to confer protection against senescence triggered by a high glucose *milieu* on human lung fibroblasts (**Zhang et al., 2016)**. It is also capable of activating SIRT1, mimicking the effects of caloric restriction, thus exerting a pro-longevity action (**Howitz et al., 2003; Schilder et al., 2009; Lam et al., 2013)**. Such effects are probably involved in metabolism improvement and ARD prevention in animal models **(Cantó et al., 2012)**.

The neuroprotective activity of resveratrol and pterostilbene demonstrated in *in vitro* and *in vivo* suggests a potential role for it in dementia prevention/treatment **(Lange and Li, 2017)**.

Vitamin B_3 complex and NAD+

B_3 vitamins are especially enriched in white meat, peanuts, and mushrooms. The family includes nicotinamide (niacinamide), niacin (nicotinic acid), and nicotinamide riboside, which are precursors of nicotinamide adenine dinucleotide (NAD). Its oxidized form, NAD^+, is a crucial cofactor in

several cellular pathways, such as energy metabolism and oxidative stress **(Fang et al., 2017)**, as well as in lifespan – through poly(ADP-ribose) polymerase, mono-ADP-ribosyltransferase, and the SIRT family **(Belenky et al., 2007)**. A low ratio of NAD^+ to NADH, its reduced form, favors senescence onset, reducing DNA repair ability and SIRT activity (**Imai and Guarente et al., 2014)**. SIRT2 reduction compromises the deacetylation of BUBR1 (mitotic checkpoint kinase budding uninhibited by benzimidazole-related 1) which, in turn, antagonizes senescence **(Wiley and Campisi, 2016)**. More recently, a form of senescence mediated by mitochondrial SIRT3 or SIRT5 depletion has been associated with a distinct secretory phenotype, a phenomenon termed MiDAS (mitochondrial dysfunction-associated senescence). Also in this case, cells undergoing senescence were characterized by a low NAD^+/NADH ratio. Consistent with these data, nicotinamide mononucleotide supplementation or forced NADH oxidation has been reported to delay senescence onset (**Wiley et al., 2016**). Notably, NAD^+ treatment is sufficient to prevent age-associated metabolic decline and to promote longevity in *C. elegans* (**Mouchiroud et al., Cell 2013)**. NAD^+ levels decline with age and may be crucial in raising the risk of ARD development; their restoration by supplementation with NAD^+ intermediates could mitigate this risk.

Other natural compounds

Other natural compounds with antioxidant activity, including phloroglucinol, ginsenosides, oleuropein, oleacein, and spermidine, have recently been suggested to possess anti-senescence activity.

Phloroglucinol

There is evidence that treatment with phloroglucinol, a phenol derivative, reduces the concentration of malondialdehyde, a reactive molecule capable of inducing oxidative stress in senescent human lung fibroblasts (**So and Cho, 2014**). A similar effect has been described in human keratinocytes exposed to UVB, where phloroglucinol reduced ROS and matrix metalloproteinase production **(Piao et al., 2012)**. Its administration also induced a reduction in the metastatic spread of breast

cancer cells both *in vitro* and in mice **(Kim et al., 2015)**. The underlying molecular mechanism may be a reduction of SLUG through inhibition of PI3K/AKT and RAS/RAF-1/ERK signaling. Since phloroglucinol exerts no known toxic effects, it may be a promising anticancer agent.

Ginsenosides

Some saponins, like ginsenosides, have been investigated for their anti-metastatic activity in human breast cancer (**Nag et al., 2012**). It has also been suggested that certain ginsenosides can prevent cartilage collagen matrix breakdown in patients with arthritis (**Lee et al., 2014**). Testing for their anti-senescence properties revealed that ginsenoside Rb1 was able to reverse the unfavorable effects of H_2O_2 treatment in HUVECs through a reduction in malondialdehyde concentrations, an increase in superoxide dismutase activity, a reduction in SA β-gal activity, and induction of SIRT1 expression (**Liu et al., 2011; Song et al., 2014**). It also restored normal conditions in human WI-38 diploid fibroblasts after induction of premature senescence with tert-butyl hydroperoxide (t-BHP). Senescent fibroblasts typically showed elevated p21 and p16 levels and reduced ATP synthesis associated with cell cycle arrest. Treatment with ginsenoside Rg1 attenuated these features and restarted the cell cycle towards the S phase, thereby delaying senescence **(Chen et al., 2008)**. In a study involving the D-galactose-induced mouse aging model, ginsenoside Rg1 also exerted neuroprotective effects, since it i) protected hippocampal stem cells by raising SOX2 levels and glutathione peroxidase and superoxide dismutase activity, thus enhancing telomerase activity and promoting telomere elongation, and ii) reduced inflammation by reducing IL-1β, IL-6 and TNF-α levels and downregulating *p53, $p21^{Cip1/Waf1}$ and $p19^{Arf}$* gene expression, ultimately inducing a general improvement in cognitive ability and neurogenesis **(Zhu et al., 2014)**. Two similar studies of D-galactose-induced mouse pancreas **(Dong et al., 2017**) and kidney **(Fan et al., 2016**) aging demonstrated that ginsenoside Rg1 ameliorated aging-related conditions, reducing senescence markers and the number of damaged cells.

Oleuropein and oleacein

Oleuropein, a phenolic compound extracted from olive oil and olive tree leaves, has been reported to exert a variety of beneficial effects **(Santiago-Mora et al., 2011; Casamenti et al., 2017)**, including anti-inflammatory, antioxidant, anticancer, and cardio- and neuroprotective actions (**Sun et al., 2017)**. An *in vitro* study found that its anti-aging effect is mainly mediated by the induction of autophagy in relation to increased AMPK phosphorylation and mTOR inhibition (**Rigacci et al., 2015**). Treatment of cultured endothelial progenitor cells with oleuropein or oleacein, a derivative of oleuropein, after senescence induction with angiotensin II was associated with a significant reduction in SA β-gal activity and ROS concentration and with increased cell replication and telomerase activity (**Santiago-Mora et al., 2011**). Treatment of pre-senescent human lung (MRC5) and neonatal human dermal (NHDF) fibroblasts with oleuropein aglycone (OLE) for 4-6 weeks reduced β-gal-positive cells, p16 protein expression, IL-6 and metalloprotease secretion, and COX type 2 (COX-2) and α-smooth actin levels **(Menicacci et al., 2017).**

As regards the effects on ARDs, oleuropein has been demonstrated to have cardioprotective, anti-ischemic, hypolipidemic, and antihypertensive activity. It can prevent oxidative stress both in the hypothalamus of spontaneously hypertensive rats (**Sun et al., 2016**) and in rabbit aorta (**Levonen et al., 2007**) through activation of the Nrf2 pathway. Since it confers protection from oxidative stress on aged rat substantia nigra, the brain region that is most affected by neurodegeneration in Parkinson's disease, a therapeutic effect on Parkinson's and Alzheimer's disease has also been hypothesized (**Sun et al., 2017)**. The ability of oleuropein to lower blood pressure justifies the traditional use of olive tree leaf to treat mild to moderate hypertension. However, it should not be administered to hypotensive individuals or to those receiving antihypertensives (**Sun et al., 2017**).

Spermidine

Spermidine is a polyamine with exceptional anti-aging properties. Its main effect, which has extensively been investigated in a number of animal models and in humans, is to induce autophagy by inhibiting histone acetylase activity. Spermidine administration was able to reduce oxidative stress in animal models **(Jeong et al., 2017**) and, coupled with exercise, it rescued atrophied

skeletal muscle from rats with D-gal-induced aging **(Fan et al., 2017)**. In addition, oral spermidine extended mouse lifespan and conferred cardioprotective effects on old mice by reducing cardiac hypertrophy and preserving diastolic function (**Eisemberg et al., 2016**), and reversed age-related cardiac deterioration in rats **(Zhang et al., 2017)**. Spermidine supplementation has also been shown to protect against neurodegeneration and cognitive decline in aged animal models. In *Drosophila* it suppressed age-dependent memory impairment by acting on the synaptic compartment (**Gupta et al., 2016**). In a very recent 3-month randomized, placebo-controlled, double-blind, phase II trial of subjects with cognitive decline, spermidine-rich plant extract proved safe and well tolerated in older adults **(Schwarz et al., 2018)**, opening the way for longer-term intervention studies in humans.

Urolithins

Urolithins are gut microbiota metabolites of ellagitannins; ellagitannin-rich foods include walnuts, red raspberries, strawberries, and pomegranates. Since urolithin A (UA) and B are able to attenuate LPS-induced inflammation, inhibiting activation of the NF-κB and Akt signaling pathways (**Xu et al., 2018**), they may emerge as new anti-SASP metabolites. It has recently been noted that oral UA can induce mitophagy both *in vitro* and *in vivo*. In *C. elegans*, UA prevented age-related accumulation of dysfunctional mitochondria and extended lifespan, whereas in rodents it improved exercise capacity both in different mouse models of age-related decline of muscle function and in young rats **(Ryu et al., 2016)**.

The anti-SASP and senolytic effects of synthetic and natural compounds are summarized in Figure 2.

3.3 Safety and efficacy of natural compounds with senolytic and/or anti-SASP properties

Despite the abundance of *in vivo* and *in vitro* data on PP-rich foods, information on their safety and efficacy is still incomplete. Two outstanding problems are the very high doses that are required to achieve biological effects and their inconsistent bioavailability in the different commercial products (**Malavolta et al., 2014**). Moreover, even though no long-term studies have demonstrated the toxic

effects of an excess of PPs, especially flavonoids, it cannot be excluded that high-concentration supplementation may induce unfavorable effects (**Skibola et al., 2000)**. Notably, excessive flavonoid intake can affect drug activity and absorption of trace elements. Since flavonoids chelate metal (iron, copper, and zinc) ions, high concentrations can reduce their levels and consequently their role in enzymatic activity, although views on the issue are contrasting **(Jaccob et al., 2012)**. High catechin levels have been reported to induce DNA damage in mouse spleen cells **(Fan et al., 2004)**, and harmful effects have been described in fibroblast and keratinocyte cell lines exposed to high concentrations of epicatechin **(Ugartondo et al., 2006**). However, since other factors such as synergistic effects and exposure duration may be involved in adverse reactions, these interactions require further investigation (**Fu et al., 2011)**.

Although several data suggest that PPs may be representative of the protective effects conferred by plant-derived foods and beverages, no human intervention studies have been performed to evaluate the effects of high-dose PPs. Since consumption of PP-rich foods may lead to mega-dose ingestion, well-designed, long-term investigations of individual PPs as well of PP-rich foods are warranted to obtain reliable information for public health recommendations on anti-aging PP treatment (**Williamson et al., 2008**). No long-term studies are currently available regarding children and elderly people.

4. Natural compounds and the immune system

SCs are considered as a source of aging-related chronic systemic inflammation, or inflammaging **(Franceschi et al., 2000**). Increasing evidence suggest that immune cells, *i.e.* natural killer (NK) cells and macrophages, are able to recognize and eliminate SCs through a mechanism of "senescence surveillance" (**Krizhanovsky et al., 2008)**. Age-related changes in the immune system, or immunosenescence, involve defective SC clearance **(Prattichizzo et al., 2018; Burton and Stolzing, 2018)** and contribute to the increased susceptibility of elderly individuals not only to infectious diseases, but also to the most common ARDs. Recently it was hypothesized that immune

cells can become dysfunctional due to SASP acquisition **(Burton and Stolzing, 2018)**. Solid evidence indicates that monocytic cell lineages, *i.e.* macrophages, can express prototypical senescence markers like p16 and SA β-gal (**Hall et al., 2016, 2017; Ong et al., 2018)**. Since the maintenance of immune cell function is a well-recognized factor in healthy aging, a variety of bioactive natural compounds have been tested on different immune cells both *in vitro* and in animal models. The effects that have been characterized most extensively in relation to aging are enhanced NK cell function and macrophage phenotype modulation.

A number of edible plants and plant products, including Echinacea, garlic, ginkgo, ginseng, and grape seed extract, inhibit COX enzyme and lipid peroxidation activity, suggesting that they can exert anti-inflammatory effects mainly by inhibiting the synthesis of pro-inflammatory mediators released by innate immune cells **(Raman et al., 2008)**. Investigation of the ability of some natural compounds to modulate macrophage polarization has demonstrated that apigenin is capable of favoring M2 macrophage polarization activating PPARγ, thus blocking p65 nuclear translocation and reducing NF-κB activation. In mouse macrophages, apigenin significantly reversed the shift from M1 to M2 and reduced the infiltration of inflammatory cells in liver and adipose tissue as well as the levels of pro-inflammatory cytokines, thus alleviating inflammation **(Feng et al., 2016)**. For instance, ω-3 fatty acids are known to possess a potent anti-inflammatory activity, antagonizing TLR receptor (**Simopoulos et al., 2002**). Similarly, epigallocatechin-3-gallate strongly inhibits NF-kB in T cells (**Aktas et al., 2004**).

Echinacea extract is known to stimulate NK cell proliferation, as demonstrated in aged mice (**Currier and Miller 2002**). Naringenin, one of the most popular flavonoids derived from citrus fruit, enhances NK activity, induces B cell proliferation, and inhibits macrophage oxidation **(Maatouk et al., 2016)**.

5 Dietary interventions

Experimental and epidemiological data indicate that dietary habits, exercise, and genetic make-up play a central role in healthy aging.

Caloric restriction (CR) is considered as a conservative mechanism to extend lifespan in organisms as diverse as yeast, worms, flies, rodents, primates, and humans **(Fontana et al., 2010; Lettieri-barbato et al., 2016; Hadem et al., 2017**; **Balasubramanian et al., 2017**). CR consists in a 25-50% calorie reduction with respect to a common diet, with preservation of the supply of vitamins and minerals. CR modulates nutrient signaling cascades such as insulin/IGF-1, mTOR, AMPK, and SIRTs, reducing oxidative stress, improving mitochondrial function, activating anti-inflammatory responses, promoting neurogenesis, and increasing synaptic plasticity **(Hadem et al., 2017)**. The beneficial effects of fasting-mimicking diet (FMD), which is low in calories, sugars, and protein but high in unsaturated fats, have recently been stressed. Cycles of five consecutive FMD days per month for three months proved safe, feasible, and effective in reducing aging and ARD markers and risk factors in humans **(Wei et al., 2017)**. However, some of the beneficial effects of CR on metabolic health should be attributed to the high-quality food consumed by practitioners, as suggested by data collected in individuals adhering to strict vegan diets (**Rizza et al., 2014)**. Notably, resveratrol has been seen to mimic the effects of CR in mice, inducing gene expression patterns that parallel those induced by CR (**Pearson et al., 2008**). Other diets besides CR have been suggested to promote healthy aging. The Mediterranean diet (MD), which is characterized by a high quota of vegetables, fruits, whole cereals, and fish, has proven beneficial effects on human health and prevents a variety of ARDs (**Sofi et al., 2008; Xavier Medina et al., 2009; Marin et al., 2012; Salas-Salvadó et al., 2016; Wade et al., 2017)**, including frailty (**Ntanasi et al., 2017**). A 10-year longitudinal study (HALE) carried out in ten European countries and involving elderly subjects with and without chronic diseases showed a significant association between MD and lifespan **(Knoops et al., 2006; Boccardi et al., 2013**). A greater MD adherence has recently been associated

with a lower incidence of cardiovascular disease and mortality in the UK, suggesting that it promotes healthy aging also in non-Mediterranean countries **(Tong et al., 2016)**.

Even though the mechanisms underpinning its beneficial and pro-longevity effects are still unclear, the MD modulates multiple interconnected processes, such as free radical production, NF-κB activation, and the SASP (**Ostan et al., 2015**). The MD has recently been conceptualized as a form of chronic hormetic stress, similar to CR (**Martucci et al., 2017**). Its ability to modulate inflammation may be mediated, as stressed above, by its content in anti-aging bioactive compounds. The findings of the PREDIMED study indicate that the MD supplemented with virgin olive oil and nuts enhanced antioxidant capacity in patients with metabolic syndrome (**Sureda et al., 2016**). Since vegetables, fruits, nuts, and olive oil are PP-rich, their anti-aging effects clearly contribute to the beneficial effects of the MD throughout life.

Studies of the dietary regimens of long-lived individuals lend support to some of the scientific data regarding the pro-longevity/anti-aging effects of specific diets (**Hausman et al., 2011**). For instance, the residents of Okinawa, the southernmost prefecture of Japan, have an extremely long life expectancy and a limited ARD incidence. Their longevity is held to be largely due to lifestyle, particularly their traditional diet, which is low in calories but rich in nutrients, especially phytonutrients (antioxidants and flavonoids) (**Willcox et al., 2009, 2014)**. Data on centenarians from Southern Italy reinforce these findings (**Vasto et al., 2014)**.

The effects of nutrients are also being assessed in terms of interactions between natural and chemical compounds and the gut microbiota (**Bhat et al., 2017)**. Food components are characterized by a two-way interaction with microbiota: i) they can directly modulate their composition **(Jung et al., 2005; Chavez et al., 2006; Xia et al., 2010; Li et al., 2014; Huanget al., 2016**), and ii) they are catabolized by the intestinal microbes to release metabolites that are more active and more easily absorbed than the native molecules (**Yoshimoto et al., 2013; Espín et al., 2017**). It is estimated that only 5–10% of the total PP intake is absorbed in the small intestine and that 90–95% accumulate in the large intestine, where they undergo enzymatic modification by the

gut microbiota (**Cardona et al., 2016**). Since increasing evidence supports the hypothesis that the gut microbiota are involved in the development of human diseases such as obesity, metabolic syndrome, diabetes, cardiovascular disease, cancer, and neurodegenerative disorders, it is conceivable that the protection against ARD development and progression, hypothesized for some anti-senescence compounds like flavonoids, is related to the effects of such molecules on the microbiota (**Singh et al., 2017)**. In turn, the gut microbiota can induce epigenetic modifications, as demonstrated in DNA methylation and histone modification of immune system cells (**Ye et al., 2017).** The ability of some flavonoids, like quercetin, resveratrol, and catechin, to regulate the gut microbiota has been documented in animal models **(Huang et al., 2016; Sung et al., 2017)**. Oral resveratrol produced taxonomic and functional changes in the gut microbiota of obese mice (**Sung et al., 2017**). Notably, fecal transplantation from healthy resveratrol-fed donor mice improved glucose homeostasis in obese mice, suggesting that resveratrol-mediated changes in the gut microbiome may play a key role in the mechanism of action of the compound (**Sung et al., 2017)**. Interestingly apples, which are rich in flavonoids, have been associated with a reduction in some inflammation markers and changes in the gut microbiota of healthy mice **(Espley et al., 2014)**.

The gastrointestinal microbiota of healthy human adults consist primarily of bacteria belonging to the phyla *Firmicutes* and *Bacteroidetes* and, to a lesser extent, to *Actinobacteria* and *Proteobacteria* (**Yang et al., 2014**). Inflammation may result in a higher level of aerobiosis and production of ROS, which inactivate the strictly anaerobic *Firmicutes* and induce blooms of facultative aerobes, commonly named "pathobionts", a condition that is frequently observed in the elderly (**Lozupone et al., 2012, Santoro et al., 2018**). Studies of animal models have shown that resveratrol modulates the ratio of *Bacteroidetes* to *Firmicutes* **(Etxeberria et al., 2015)**. In overweight men and women, combined PP supplementation was associated with a significant decrease in *Bacteroidetes* that was greater in men (**Most et al., 2017**). The demonstration that quercetin can modulate the gut microbiota composition suggests that it has therapeutic potential in some human diseases (**Dueñas**

et al., 2015; Porras et al., 2017). A recent study describes the relationship between fecal quercetin metabolism, human microbiota, and dietary intake in elderly subjects (**Tamura et al., 2017**).

Therefore, some foods can produce predictable shifts in existing host bacterial genera and can be harnessed to change their composition **(Dueñas et al., 2015; Most et al., 2017)**. Since PPs are found in plant-based foods and beverages such as apples, berry and citrus fruit, plums, and broccoli, the inclusion of phenol-rich foods in the diet is consistent with the advice to eat five or more portions of fruit and vegetables per day **(Williamson, 2017).**

6. Concluding remarks and future perspectives

A new scientific discipline, nutrigerontology, examines the impact of nutrients, foods, macronutrient ratios, and dietary habits on the ability to achieve successful aging and longevity (**Verburgh et al., 2015; Aiello et al., 2016)**. Of course, this goal entails not only avoiding all those factors that promote senescence, but also seeking foods whose components can help delay the aging process. The comprehensive information on the different classes of molecules, provided above, demonstrates that some natural components share the same mechanisms of action with conventional medications, and that natural molecules with anti-SASP and/or senolytic activity are naturally available through the diet, for instance the MD. Although considerable work is still required to explore the toxicity profile and the extent of the benefits provided by natural compounds, there is mounting evidence that nutritional approaches provide new tools to combat ARDs, including cognitive decline (**Poulose et al., 2017**).

Exosomes – vesicles measuring 30–100 nm in diameter derived from multivesicular bodies – contain a number of molecules such as DNA, mRNA, non-coding RNAs, and proteins. They are found in all living organisms and can shuttle bioactive molecules to other organisms. The ability of exosomes to carry and release their cargo could be exploited as a sort of nanoplatform to deliver drugs including senolytic and anti-SASP molecules (**Liu et al., 2017**). Since they are also found in

food, including milk, their potential role in the promotion of immune regulatory functions is under investigation (**Izumi et al., 2015**)

As noted above, the execution of senescence programs induces the appearance of characteristics that enable SC identification both *in vitro* and *in vivo* (**Kuilman et al., 2010**). Demonstration of the effectiveness of anti-senescence compounds should first be achieved through *in vitro* studies and subsequently confirmed *in vivo*, to evaluate their effects on the salient features of SCs. However, no long-term human studies have yet been conducted to assess the pharmacodynamics, pharmacokinetics, and especially the toxicity of repeated exposure to senolytic compounds. Cell culture studies have provided valuable information on their mechanisms of action and effective concentrations (usually micro-molar). However, human studies are hampered by the fact that after ingestion molecules interact with multiple biological structures, undergo a variety of modifications, and are subject to a wide range of influences; among these, crucially, inactivation or creation of toxic metabolites through the metabolism and/or microbiota. Some studies have found that these molecules increase lifespan and delay ARD development in animals such as worms, flies, and mice. Over the next few years, several more molecules that can extend animal lifespan are likely to be discovered. However, two important problems remain to be addressed: i) the lack of pharmacological data, especially long-term ones, on the safety and efficacy of senolytics in humans in view of the development of supplements and nutraceuticals with senolytic activity; and ii) the lack of data on the ability of senolytic compounds to prevent or cure chronic human diseases.

Since clinical trials with long-term endpoints such as lifespan or healthspan are not feasible, new paradigms for testing senolytics and measuring surrogate endpoints of aging should be identified (**Niedernhofer et al., 2017 ARR**). Notably, senolytic treatment does not necessarily need to be continuous, as demonstrated in mice models where periodic SC removal slowed the progression of the major ARDs **(Kirkland et al., 2017 a/bce ne sono 2 di Kirkland 2017)**. It has also been suggested that senolytics should be tested in patients with multimorbidity, accelerated aging-like conditions, diseases involving localized SCs accumulation, age-related loss of physiological

resilience, and frailty. Therapeutic strategies that safely contribute to selective SCs elimination or SASP restraint are attracting increasing attention, with some programs now nearing human clinical study **(Kirkland et al., 2017b; Childs et al., 2017; Scudellari et al., 2018)**.

We believe that the adoption of an anti-senescence diet should be a life-long endeavor, whereas approaches based on senolytics, if they are proved to be effective and safe in clinical trials, may be applied to extend healthspan.

Conflicts of Interest

Declarations of interest: “none”.

Authors’ Contributions

Felicia Gurău, Simone Baldoni, and Francesco Prattichizzo wrote the paper, which was revised by Fabiola Olivieri. Francesco Amenta and Antonio Domenico Procopio revised data on senolytic compounds; Emma Espinosa and Massimiliano Bonafè revised data on anti-senescence compounds and ARDs and Cristina Albertini revised data on natural compounds and the immune system, as well as on natural compounds and dietary intervention.

Acknowledgments

This study was supported by grants from UNIVPM to FO and ADP, and by grants to FO from POR MARCHE FESR 2014 - 2020 - PRINTAGE projects.

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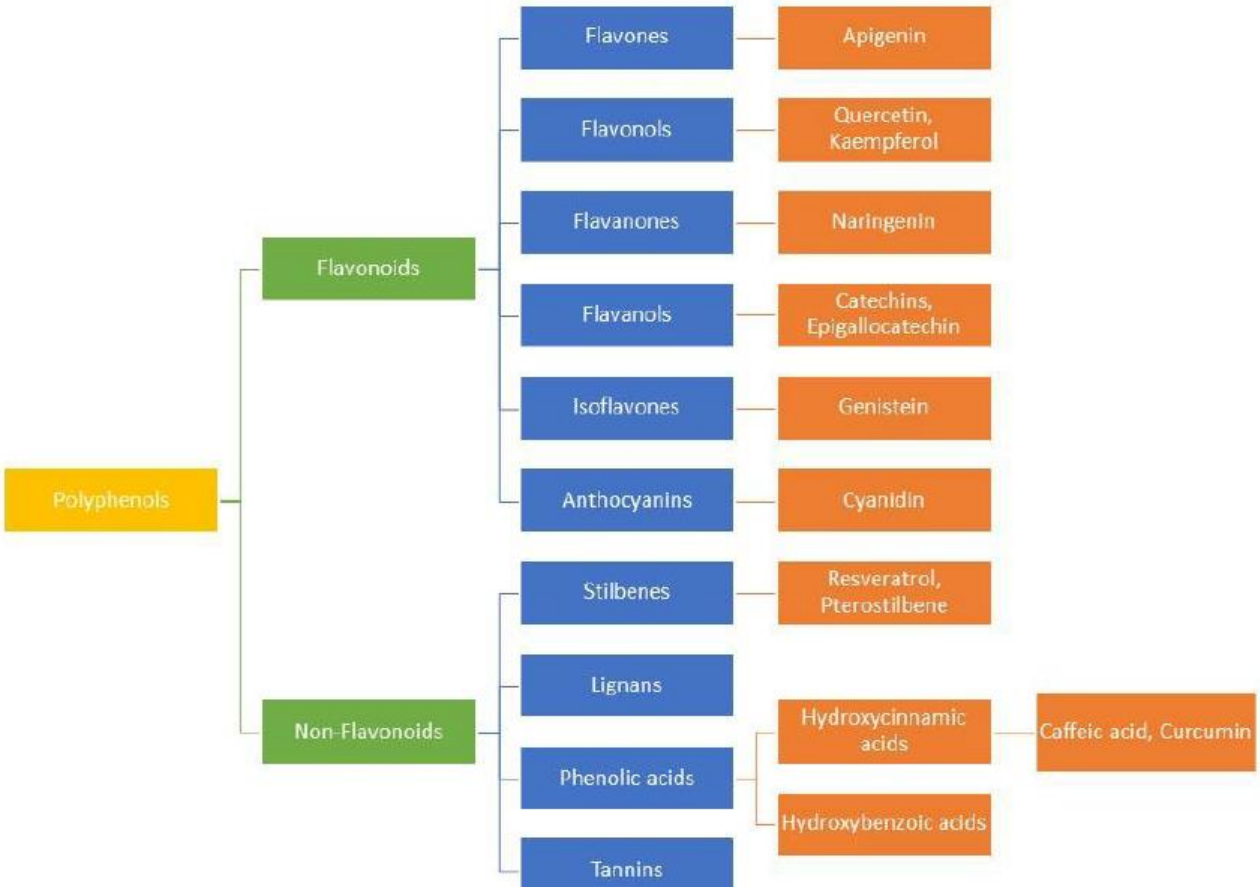
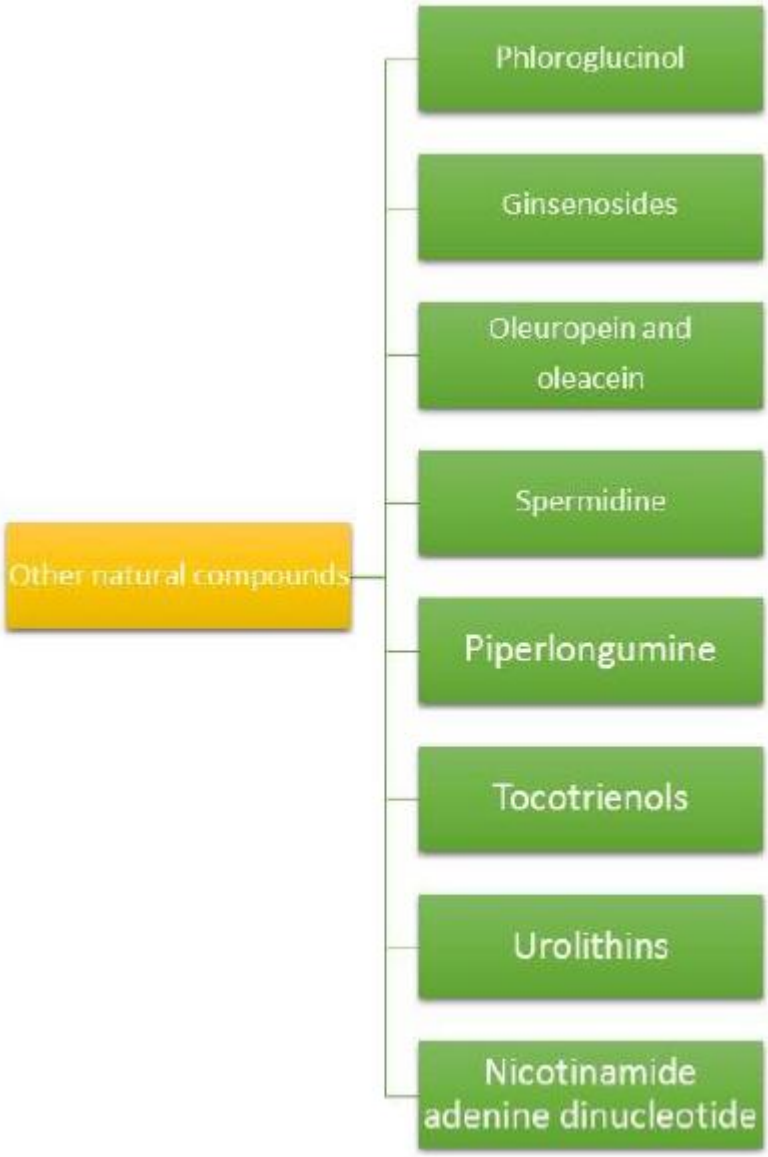

Polyphenols
Flavonoids
Non-Flavonoids
Flavones
Apigenin
Flavonols
Quercetin, Kaempferol
Flavanones
Naringenin
Flavanols
Catechins, Epigallocatechin
Isoflavones
Genistein
Anthocyanins
Cyanidin
Stilbenes
Resveratrol, Pterostilbene
Lignans
Phenolic acids
Hydroxycinnamic acids
Caffeic acid, Curcumin
Hydroxybenzoic acids
Tannins


Other natural compounds
Phloroglucinol
Ginsenosides
Oleuropein and oleacein
Spermidine
Piperlongumine
Tocotrienols
Urolithins
Nicotinamide adenine dinucleotide

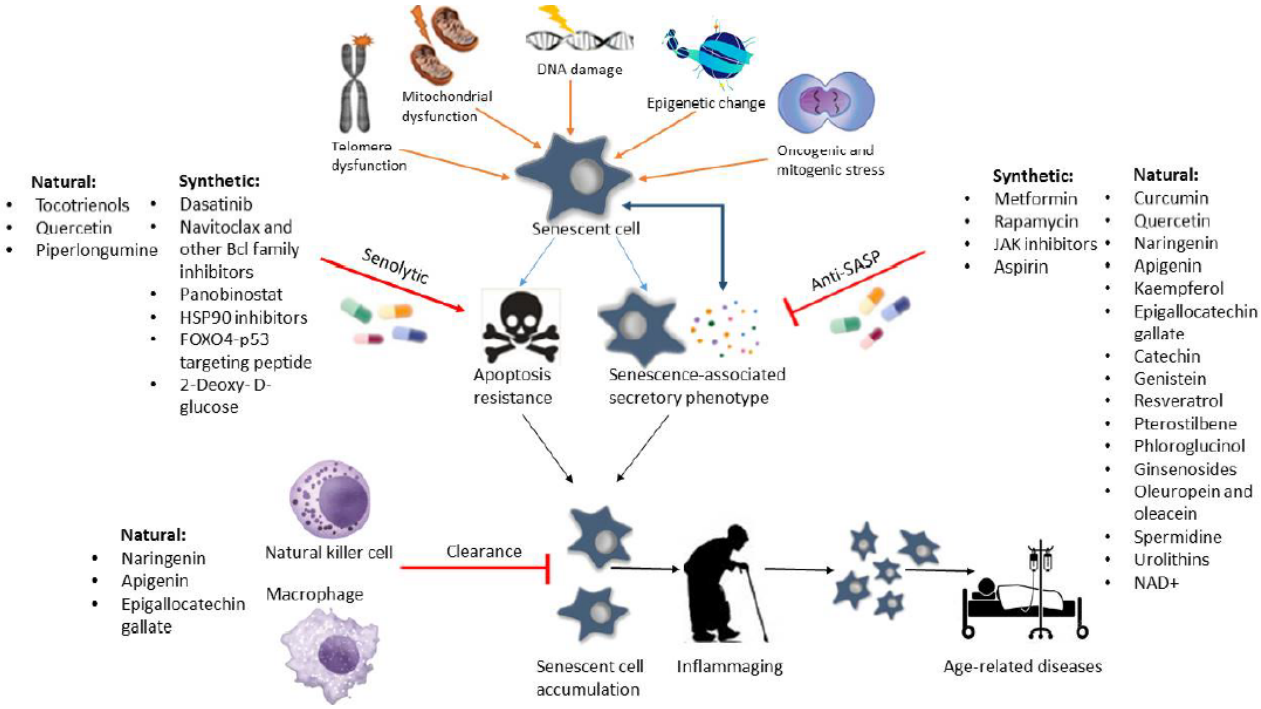

Natural:
Tocotrienols
Quercetin
Piperlongumine
Synthetic:
Dasatinib
Navitoclax and other Bcl family inhibitors
Panobinostat
HSP90 inhibitors
FOXO4-p53 targeting peptide
2-Deoxy- D-glucose
Telomere dysfunction
Mitochondrial dysfunction
DNA damage
Epigenetic change
Oncogenic and mitogenic stress
Senescent cell
Senolytic
Anti-SASP
Apoptosis resistance
Senescence-associated secretory phenotype
Synthetic:
Metformin
Rapamycin
JAK inhibitors
Aspirin
Natural:
Curcumin
Quercetin
Naringenin
Apigenin
Kaempferol
Epigallocatechin gallate
Catechin
Genistein
Resveratrol
Pterostilbene
Phloroglucinol
Ginsenosides
Oleuropein and oleacein
Spermidine
Urolithins
NAD+
Natural:
Naringenin
Apigenin
Epigallocatechin gallate
Natural killer cell
Macrophage
Clearance
Senescent cell accumulation
Inflammaging
Age-related diseases

Table 1A. Foods containing the highest concentrations of polyphenols with putative anti-senescence activity

Polyphenols	Common sources	Mean content
Quercetin	Mexican oregano, dried	42.00 mg/100 g
	Black elderberry	42.00 mg/100 g
	Capers	32.82 mg/100 g
	Cloves	28.40 mg/100 g
	Chocolate, dark	25.00 mg/100 g
	Onion [Red], raw	1.31 mg/100 g
	Bilberry, raw	1.27 mg/100 g
Naringenin	Grapefruit, pure juice	1.56 mg/100 ml
	Mexican oregano, dried	372.00 mg/100 g
Apigenin	Marjoram, dried	4.40 mg/100 g
	Italian oregano, fresh	3.50 mg/100 g
	Common sage, fresh	2.40 mg/100 g
	Olive oil, extra virgin	*1.17 mg/100 g
Kaempferol	Capers	104.29 mg/100 g
	Cumin	38.60 mg/100 g
	Cloves	23.80 mg/100 g
	Caraway	16.40 mg/100 g
	Common bean [Black], whole, raw	1.80 mg/100 g
Curcumin	Turmeric, dried	*2213.57 mg/100 g
	Curry, powder	285.26 mg/100 g
Resveratrol	Muscadine grape, red wine	3.02 mg/100 ml
	Lingonberry, raw	3.00 mg/100 g
	European cranberry	1.92 mg/100 g

	Redcurrant, raw	1.57 mg/100 g
Genistein	Soy, tofu, fermented	*9.68 mg/100 g
	Soy, meat	*5.22 mg/100 g
	Soy, flour	*3.62 mg/100 g
Cyanidin	Common bean [Black], whole, raw	1.63 mg/100 g
	Red raspberry, raw	0.53 mg/100 g
Epigallocatechin 3-O-gallate	Tea [Green], infusion	*27.16 mg/100 ml
	Tea [Black], infusion	*9.12 mg/100 ml
	Pecan nut	2.30 mg/100 g
	Hazelnut, raw	1.10 mg/100 g
Caffeic acid	Black chokeberry	141.14 mg/100 g
	Spearmint, dried	*25.00 mg/100 g
	Ceylon cinnamon	24.20 mg/100 g
	Star anise	20.20 mg/100 g
	Italian oregano, fresh	10.40 mg/100 g
	Plum, prune, juice from concentrate	5.10 mg/100 ml
Catechin	Cocoa, powder	*107.75 mg/100 g
	Plum, prune, pure juice	24.70 mg/100 ml
	Broad bean seed, whole, raw	12.83 mg/100 g
	Pecan nut	7.20 mg/100 g
	Wine [Red]	*6.81 mg/100 ml
	Pistachio	3.50 mg/100 g

Data from the Phenol-Explorer database (**Phenol-Explorer: an online comprehensive database on polyphenol content in foods**. http://www.phenol-explorer.eu.)

*Mean values from several studies

Table 1B. Foods containing the highest concentrations of bioactive compounds with putative anti-senescence activity

Other bioactive compounds	Common sources	References
Phloroglucinol	Secondary metabolite found in a variety of marine organisms, especially brown (*Ecklonia stolonifera*, *Eisenia bicyclis*), and bacteria (*Pseudomonas fluorescens*)	(Achlear et al., 2005; Balboa et al., 2013)
Ginsenosides	Saponins, found in a large amount of ginseng plants (*Panax ginseng*)	(Attele et al., 1999)
Oleuropein and oleacein	Phenolic constituents of olive oil, olive tree leaves and argan oil	(Naruszewicz et al., 2015; Charrouf et al., 2007)
Spermidine	Polyamine compound found in high concentrations in dry soybean, chicken liver, green peas, corn, and shellfish.	(Atiya Ali et al., 2011)
Piperlongumine	Natural alkaloid extracted from the Piper (*Piper longum*) fruit.	(Wang Y et al., 2016)
Tocotrienols	Members of the vitamin E family, which consists of four isomers, α-, β-, δ- and γ tocopherols.	(Durani LW et al., 2015)
Urolithins	Human microflora metabolites of dietary ellagic acid derivatives, such as ellagitannins.	(Xu et al., 2018)
Nicotinamide adenine dinucleotide (NAD+)	Cofactor for several biological pathways such as cellular energy metabolism and oxidative stress.	(Fang EF et al., 2017)