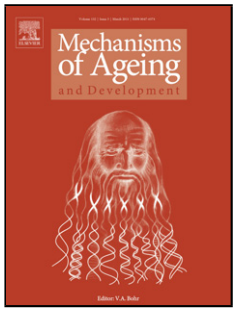

Title: Emerging senolytic agents derived from natural products

Authors: Wen Li, Lin Qin, Rennan Feng, Guangrong Hu, Hui Sun, Yonghan He, Rongping Zhang

PII: S0047-6374(19)30047-8
DOI: https://doi.org/10.1016/j.mad.2019.05.001
Reference: MAD 11117

To appear in: *Mechanisms of Ageing and Development*

Received date: 7 March 2019
Revised date: 5 April 2019
Accepted date: 7 May 2019

Please cite this article as: Li W, Qin L, Feng R, Hu G, Sun H, He Y, Zhang R, Emerging senolytic agents derived from natural products, *Mechanisms of Ageing and Development* (2019), https://doi.org/10.1016/j.mad.2019.05.001

Emerging senolytic agents derived from natural products

Wen Li[1,2,#], Lin Qin[1,3,#], Rennan Feng[4], Guangrong Hu[5], Hui Sun[5], Yonghan He[6,*], Rongping Zhang[1,*]

[1] School of Pharmaceutical Science and Yunnan Key Laboratory of Pharmacology for Natural Products, Kunming Medical University, Kunming, Yunnan 650500, China

[2] Department of Endocrinology, The Third People's Hospital of Yunnan Province, Kunming, Yunnan 650011, China

[3] Department of Endocrinology, The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650000, China

[4] Department of Nutrition and Food Hygiene, School of Public Health, Harbin Medical University, Harbin, Heilongjiang 150081, China

[5] Department of Emergency, the Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150081, China

[6] State Key Laboratory of Genetic Resources and Evolution, Kunming Institute of Zoology, the Chinese Academy of Sciences, Kunming 650223, China*****

* Correspondence: zhrpkm@163.com, Tel: +86-871-65922812;
heyonghan-2008@163.com, Tel: +86-871-68125401

# These authors have contributed equally to this work.

Highlights

- Cellular senescence is a hallmark of aging and driven factor for age-related diseases
- Cellular senescence is a novel therapeutic target for aging and age-related diseases
- Senolytics are able to eliminate senescent cells to delay aging and extend healthspan
- Natural senolytics have great potential to be translated to clinic

Abstract

Cellular senescence is a hallmark of aging, it is a permanent state of cell cycle arrest induced by cellular stresses. During the aging process, senescent cells (SCs) increasingly accumulate in tissues, causing a loss of tissue-repair capacity because of cell cycle arrest in progenitor cells and produce proinflammatory and matrix-degrading molecules which are known as the senescence-associated secretory phenotype (SASP), and thereby contribute to the development of various age-related diseases. Genetic evidence has demonstrated that clearance of SCs can delay aging and extend healthspan. Senolytics, small molecules that can selectively kill SCs, have been developed to treat various age-related diseases. In recent years, emerging natural compounds have been discovered to be effective senolytic agents, such as quercetin, fisetin, piperlongumine and the curcumin analog. Some of the compounds have been validated in animal models and have great potential to be pushed to clinical applications. In this review, we will discuss cellular senescence and its potential as a target for treating age-related diseases, and summarize the known natural compounds as senolytic agents and their applications.

Keywords: Aging; Cellular senescence; Natural compounds; Senolytic agent

1. Introduction

Aging is an irreversible process characterized by a progressive loss of physiological integrity, causing impaired function and increased vulnerability to death (López-Otín et al., 2013). It has been shown to be the primary risk factor for major age-related diseases, such as cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. The hallmarks of aging, such as cellular senescence, genomic instability, telomere attrition, epigenetic alterations, and mitochondrial dysfunction, have been described previously (López-Otín et al., 2013). Accumulating evidence suggests that targeting some of the aging hallmarks, for example, cellular senescence, can significantly improve human health and extend healthspan (Childs et al., 2017; He and Sharpless, 2017; Kirkland and Tchkonia, 2017; Naylor et al., 2013; Niedernhofer and Robbins, 2018).

Cellular senescence is a phenomenon where normal cells stop dividing. Senescent cells (SCs) accumulate in various tissues during the aging process. On one hand, cellular senescence blocks the propagation of damaged cells in order to maintain tissue homeostasis (Demaria et al., 2014). On the other hand, it plays a causative role in irreparable, deleterious cellular damage and loss of tissue homeostasis, which relates to aging and aging-associated diseases (Campisi and d'Adda di Fagagna, 2007). Accumulating evidence demonstrates that elimination of SCs can reduce age-dependent deterioration in tissues and organs, which is useful in improving the treatment of age-associated diseases and alleviating the side effects of therapy-induced senescence (Baker et al., 2011; Campisi and d'Adda di Fagagna, 2007; Childs et al., 2015; He and Sharpless, 2017; Kirkland and Tchkonia, 2017; Naylor et al., 2013; Niedernhofer and Robbins, 2018).

Small molecules that can selectively kill SCs, called senolytics, have the potential to both prevent and treat age-related diseases, thereby extending healthspan. Until now, several classes of senolytic agents, including natural compounds such as quercetin (Geng et al., 2018; Hwang et al., 2018; Zhu et al., 2015), fisetin (Yousefzadeh et al., 2018), piperlongumine (Y. Wang et al., 2016; Zhang et al., 2018), and curcumin analog EF24 (Li et al., 2019), and targeted therapeutics, which are mainly senolytic target inhibitors, have been identified. Compared to the targeted senolytics, natural senolytic compounds are less potent, but have

low toxicity. They may also have a better chance of being translated into the clinical setting to treat age-related diseases or used as a lead for the development of more specific and potent senolytic agents. In this review, we summarize the natural senolytic compounds and their applications in eliminating SCs.

2. Cellular senescence

In 1961, Leonard Hayflick and Paul Moorhead first discovered that normal human fibroblasts have a finite proliferative capacity in culture (Hayflick and Moorhead, 1961), coined as "cellular senescence", and hypothesized that it might be an underlying cause of aging. Later, it was uncovered that this kind of cellular senescence (replicative senescence) was due to the loss of telomeres after extensive proliferation in the absence of endogenous telomerase activity (Sharpless and Sherr, 2015). Indeed, *in vitro* senescence can be induced by different damaging stimuli, such as DNA damage, oncogene induction, oxidative stress, chemotherapy, mitochondrial dysfunction and epigenetic changes (Hernandez-Segura et al., 2018). A key feature of *in vitro* senescence is the enlarged and irregularly shaped cell body, which is associated with the activation of mTOR (Bent et al., 2016) and ATF6α pathways (Cormenier et al., 2018; Druelle et al., 2016). In addition, SCs display increased lysosomal content, accumulation of mitochondria, enlarged nuclear size and increased DNA damage (Hernandez-Segura et al., 2018). Based on these changes, scientists identified a series of senescence markers, such as increased p16 and beta-galactosidase activity, to detect cellular senescence (Childs et al., 2017).

An increasing body of evidence demonstrates that cellular senescence plays an important role in tissue remodeling, injury, and repair both in normal development and physiology and in various pathological conditions and diseases (Childs et al., 2017; He and Sharpless, 2017; Hernandez-Segura et al., 2018; Naylor et al., 2013). Transient induction of senescence during the acute phase of tissue injury is presumably beneficial. SCs can help tissue repair by recruiting immune cells to clear damaged cells and stimulating the proliferation and differentiation of neighboring cells including tissue stem and progenitor cells to repopulate

the damaged tissue through secreting senescence-associated secretory phenotype (SASP) (Demaria et al., 2014). Cellular senescence is also a mechanism to suppress tumor occurrence. However, excessive and aberrant accumulation of SCs in tissues can negatively affect regenerative capacities and create a proinflammatory environment favorable for the onset and progression of various age-related diseases, including cancer. Therefore, cellular senescence is a double-edged sword, especially in fighting against cancer. Inhibiting the induction of senescence is detrimental, but elimination of SCs after detrimental stimuli may be beneficial. Besides cancer, cellular senescence is associated with many other diseases, termed senescence-related diseases, including organ fibrosis, atherosclerosis, obesity, type 2 diabetes, neurological, muscle disorders and osteoarthritis, which was described previously (Muñoz-Espín and Serrano, 2014). Therefore, both pro-senescent and anti-senescent approaches can be desirable, depending on the therapeutic context.

3. Cellular senescence as a therapeutic target

Although cellular senescence is known to be involved in aging, whether SCs are causally implicated in age-related dysfunction, and whether their removal is beneficial had remained unclear until 2011 (Baker et al., 2011). To examine the role of cellular senescence in aging and age-related pathologies, Baker *et al*. designed a transgenic strategy for the clearance of SCs in mice and demonstrated that elimination of SCs using the genetic method can significantly delay the onset of age-related pathologies and extend healthspan, providing the first evidence that cellular senescence is causally implicated in generating age-related phenotypes (Baker et al., 2011). Later, they further demonstrated that clearance of SCs delayed tumorigenesis and attenuated age-related deterioration of several organs without apparent side effects (Baker et al., 2016). Furthermore, they reported that senescent intimal foam cells are deleterious at all stages of atherosclerosis and using transgenic and pharmacological approaches to eliminate SCs hold promise for the treatment of atherosclerosis (Childs et al., 2016). Consistently, Demaria *et al*. generated a mouse model in which SCs can be visualized and eliminated in living animals, and demonstrated the

beneficial role of SCs and their SASP in tissue repair (Demaria et al., 2014). Therefore, pro-senescent therapies can be useful for the treatment of age-related diseases and for ongoing tissue repair processes (Demaria et al., 2014), whereas anti-senescent therapies may be beneficial to eliminate senescence and fibrosis in 'resolved' injuries or to rejuvenate the tissues (Figure 1). Above all, the evidence from genetic animal models suggest that cellular senescence can be a therapeutic target for aging and age-related diseases.

4. Senolytics

Clearance of SCs by genetic methods prompted a gold rush in the discovery of small molecules that can selectively kill SCs without depending on a transgene. These molecules are called "senolytics" which is from the words "senescence" and "lytic" (destroying). To date, a series of senolytic agents have been identified to target SCs, including targeted therapeutics such as dasatinib (Zhu et al., 2015), a non-specific tyrosine kinase inhibitor; inhibitors of the anti-apoptotic Bcl-2 family proteins (Chang et al., 2016; Yosef et al., 2016; Zhu et al., 2016), HSP90 and histone deacetylase (Fuhrmann-Stroissnigg et al., 2017); UBX101 (Jeon et al., 2017), an inhibitor of the MDM2/p53 protein interaction; and a modified FOXO4-p53 interfering peptide (IP) (Baar et al., 2017). In addition, cytotoxic agents encapsulated with β(1,4)- galacto- oligosaccharides have also been used to target SCs that have a high level of lysosomal β- galactosidase activity (Muñoz-Espín et al., 2018). In this review we will just briefly touch on the targeted senolytics as they were well summarized elsewhere (Childs et al., 2017). Of notice is that emerging natural compounds such as quercetin (Justice et al., 2019; Zhu et al., 2015), fisetin (Yousefzadeh et al., 2018; Zhu et al., 2017) and piperlongumine (Y. Wang et al., 2016; Zhang et al., 2018) are discovered to be effective senolytic agents. Recently we reported that EF24, a novel curcumin analog, to be another senolytic agent (Li et al., 2019). Because most of these senolytic agents come from food or other natural products, they have the advantage of low toxicity and have great potential to be translated into clinical applications. Here we will focus on discussing the new natural senolytics and their applications in treating or delaying age-related diseases.

5. Senolytic agents derived from natural product

Many natural compounds have been reported to have effects of anti-aging or age-related diseases, such as resveratrol (Knutson and Leeuwenburgh, 2008), berberine (Xu et al., 2017), rutin (Li et al., 2016; Yang et al., 2012), catechin (Assuncao and Andrade, 2015; Bernatoniene and Kopustinskiene, 2018), proanthocyanidin (Liu et al., 2018), ginkgo biloba extract (EGb 761) (Sastre et al., 1998) and other phytomolecules (Mukherjee et al., 2011). Most of them are antioxidants, but not all were reported to reduce the viability of SCs. For example, Yousefzadeh *et al*. tested a panel of flavonoids, including resveratrol, fisetin, luteolin, rutin, epigallocatechin gallate, curcumin, pirfenidone, myricetin, apigenin, catechin, and quercetin, of which fisetin was shown to have good senolytic activity, luteolin and curcumin showed weak senolytic activity while the others were not able to reduce the viability of SCs (Yousefzadeh et al., 2018). Many of the compounds exert their anti-aging functions mainly by reducing the oxidative damage levels in certain organs instead of through killing SCs, which therefore were not categorized as senolytic agents in this review. We believe that more and more natural compounds will be discovered to be effective senolytic agents in the near future. Here we focus on summarizing both the classical function and the new senolytic activities of the reported senolytic agents from natural products.

5.1 Quercetin, an attractive flavonol

Quercetin is one of the most studied dietary flavonoid ubiquitously present in various vegetables as well as in tea and red wine (Formica and Regelson, 1995). Quercetin has wide bio-activities, such as anti-oxidant, anti-obesity, anti-carcinogenic, anti-viral, anti-bacterial and anti-inflammatory (Anand David et al., 2016). Accordingly, quercetin is now largely utilized as a nutritional supplement and as a phytochemical remedy for a variety of diseases like diabetes, obesity, and circulatory dysfunction, including inflammation, as well as mood disorders. The most obvious feature of quercetin is its strong antioxidant activity which potentially enables it to quench free radicals from forming resonance-stabilized phenoxyl radicals. However, chemical instability, poor water solubility and low bioavailability of

quercetin greatly limit its applications (W. Wang et al., 2016). However, delivery systems have been utilized to improve its stability, efficacy and bioavailability.

The bio-activities and clinical applications of quercetin are well summarized elsewhere (Boots et al., 2008; Formica and Regelson, 1995); here we will focus on its senolytic activity. Oxidative stress levels increase with progression of the aging process, and given that quercetin is a strong antioxidant, people hypothesize that quercetin may delay aging via reducing oxidative stress levels. Chronic quercetin treatment can reverse cognitive deficits in aged and ethanol-intoxicated mice, which is associated with its antioxidant property (Singh et al., 2003). In 2007, it was reported that quercetin increases oxidative stress resistance and longevity in *Saccharomyces cerevisiae* (Belinha et al., 2007). The data suggests the potential of quercetin in delaying aging and extending lifespan. It has been demonstrated that the healthspan of mice can be enhanced by killing SCs. In 2015, quercetin was first found to be a senolytic agent that can effectively kill senescent human endothelial cells and mouse bone marrow-derived mesenchymal stem cells (BM-MSCs) (Zhu et al., 2015). Later, quercetin was used as a geroprotective agent against both accelerated and natural aging in hMSCs (Geng et al., 2018), providing a potential therapeutic intervention for treating age-associated disorders. However, quercetin has to be combined with dasatinib to show good senolytic activity (Zhu et al., 2015).

5.2 Fisetin

Fisetin is another flavonoid which exists in various fruits and vegetables such as apples, grapes, persimmons, strawberries, cucumbers, and onions (Arai et al., 2000). The average dietary intake of naturally occurring fisetin in Japan is approximately 0.4 mg/day (Arai et al., 2000; Kimira et al., 1998), apparently without any adverse effects. It has been reported that fisetin can exert numerous beneficial biological activities, including anti-tumor, anti-oxidant, anti-inflammatory, anti-angiogenic, hypolipidemic and neuroprotective effects (Khan et al., 2013; Pal et al., 2016; Sundarraj et al., 2018). The ability of flavonoids to scavenge free radicals confer them marked antioxidant activity and significant biological effects. The anti-

oxidative effect of fisetin have been evaluated by both cyclic voltammetry and quantum-chemical-based calculations (Khan et al., 2013; Marković et al., 2009). Emerging data have demonstrated that fisetin has good anti-tumor activity by inhibiting cancer cell proliferation, inducing cancer cell apoptosis, in a variety of cancer cell lines (Kashyap et al., 2018; Lall et al., 2016). Interestingly, the fisetin mediated anti-proliferative and proapoptotic effects were limited to cancer cells, and normal cells were much less affected by fisetin treatment (Lall et al., 2016), showing good selectivity between normal and cancer cells.

Fisetin is widely available as a nutritional supplement and has a highly favorable side-effect profile. In 2017, fisetin was first discovered to selectively induce apoptosis in SCs but not in proliferating human umbilical vein endothelial cells (HUVECs) (Zhu et al., 2017). However, it is not senolytic in senescent IMR90 cells, a human lung fibroblast strain, or primary human preadipocytes (Zhu et al., 2017), suggesting that it is a cell-specific senolytic agent. Later, the senolytic activity was validated by an in-vivo study in which a panel of flavonoid polyphenols were screened for senolytic activity using senescent murine and human fibroblasts (Yousefzadeh et al., 2018). Of the flavonoids tested, fisetin was the most potent senolytic agent that can reduce senescence markers in multiple tissues. Consistent with the *in vitro* result, fisetin reduced senescence within a subset of cells in murine and human adipose tissue, demonstrating its cell-type specificity.

5.3 Piperlongumine, an active alkaloid

Piperlongumine is a biologically active component from *Piper* species. It is the major alkaloid from long peppers and is also found in other important medicinal plants (Bezerra et al., 2013). Piperlongumine has been reported to have wide pharmacological activities, such as anti-tumor, anti-angiogenic, anti-metastatic, anti-platelet aggregation, anti-nociceptive, anti-depressant, anti-atherosclerotic, anti-diabetic, and anti-bacterial (Bezerra et al., 2013). Particularly, its anti-cancer activities has been extensively studied by different research groups. Specifically, piperlongumine can kill various cancer types, including leukemia and solid tumors, such as colon, skin, breast, lung, central nervous system (CNS), pancreatic, nasopharyngeal, osseous, bladder, renal, and prostate cancers (Bezerra et al., 2013; Piska et

al., 2018). Of notice is that its cytotoxicity was limited to tumor cells in the micromolar range without causing toxicity to normal cells (Bezerra et al., 2013). This compound showed selective cytotoxicity over cancer cells and presents only weak activity in normal cells. For example, piperlongumine was able to suppress leukemia growth and reduce cell viability by triggering cell apoptosis, however, only weak cytotoxicity was observed in normal lymphocytes (Bezerra et al., 2007). Besides affecting cell death and cell cycle, piperlongumine can also regulate signal transduction pathways, such as receptor tyrosine kinase (Raf-1) and extracellular signal-regulated kinases (ERK1/2) (Bezerra et al., 2013). In addition, piperlongumine can suppress tumor progression and migration. Piperlongumine induces cell death selectively in tumor cells, possibly by its effects on oxidative stress response enzymes such as GSTp1 and CRB1 (Bezerra et al., 2013).

By screening a small library of structurally diverse, rationally-selected small molecules that target pathways predicted to be important for the survival of SCs, we identified piperlongumine as a promising novel lead for the development of senolytic agents (Y. Wang et al., 2016). Piperlongumine preferentially killed senescent human WI-38 fibroblasts induced by ionizing radiation, replicative exhaustion, or ectopic expression of the oncogene *Ras*. Pretreatment of the pan-caspase inhibitor Q-VD-OPh (QVD) can significantly block the apoptosis induced by piperlongumine, suggesting the involvement of caspase in the cell death caused by piperlongumine. Interestingly, unlike in some cancer types, piperlongumine killed SCs by inducing apoptosis without inducing the production of reactive oxygen species (ROS) (Y. Wang et al., 2016). In addition, we found that piperlongumine synergistically killed SCs in combination with ABT-263, a Bcl-2/Bcl-xL inhibitor. Initial structural modifications to piperlongumine identified analogs with improved potency and/or selectivity in inducing SC death. However, the targets of piperlongumine are largely unknown. Later, we used a piperlongumine-based chemical probe to pull-down piperlongumine-binding proteins from live cells and then performed a mass spectrometry-based proteomic analysis to identify potential molecular targets of piperlongumine in SCs. One prominent target was oxidation resistance 1 (OXR1), an important antioxidant protein that regulates the expression of a variety of antioxidant enzymes. We found that OXR1 was upregulated in senescent human

WI38 fibroblasts. Piperlongumine was bound to OXR1 directly and induced its degradation through the ubiquitin-proteasome system in an SC-specific manner (Zhang et al., 2018). These findings provide new insights into the mechanism by which SCs are highly resistant to oxidative stress and suggest that OXR1 is a novel senolytic target of piperlongumine that can be further exploited for the development of new senolytic agents.

5.4 EF24, a novel curcumin analog

Besides the aforementioned natural compounds, many others have been identified for medicinal purposes (Harvey, 2008; He et al., 2014, 2013; Molinski et al., 2009; Newman and Cragg, 2016). Curcumin, a hydrophobic polyphenol derived from the rhizome of the herb *Curcuma longa,* is a well-defined one. Curcumin has been demonstrated to have wide-spectrum biological and pharmacological activities, such as anti-cancer, anti-inflammation, anti-oxidation, and anti-microbial, which was summarized previously (Aggarwal and Harikumar, 2009; Anand et al., 2008; Gupta et al., 2013; Hatcher et al., 2008; Maheshwari et al., 2006). Many researches have studied the therapeutic potential of curcumin and showed the beneficial aspects of curcumin in delaying aging and the prevention and treatment of age-associated diseases (Grill et al., 2018; Takano et al., 2018; Yang et al., 2017). Moreover, curcumin was shown to prolong lifespan and extend health span in *Drosophila melanogaster* (fruit fly) (Chandrashekara et al., 2014) and *Caenorhabditis elegans* (Liao et al., 2011). However, one potential problem hindering the clinical use of curcumin is its low potency and poor absorption characteristics (Shoba et al., 1998). Indeed, curcumin itself was reported to show weak senolytic activity by a recent study (Yousefzadeh et al., 2018). To improve the bioavailability and biological efficiency of curcumin, a series of curcumin analogs were developed, such as EF24 (Adams et al., 2005; He et al., 2018), HO-3867 (Selvendiran et al., 2009), 2-HBA (Dinkova-Kostova et al., 2007) and Dimethoxycurcumin (DIMC) (Tamvakopoulos et al., 2007), which were shown to be more active over curcumin in reducing age-dependent deterioration (such as cancer, inflammation, et al).

Recently, from these curcumin analogs, we identified EF24 as the most potent senolytic agent (Li et al., 2019). EF24 reduced cell viability not only in ionizing radiation induced SCs,

but also in SCs induced by extensive replication or ectopic transfection of the *Ras* oncogene. More importantly, EF24 has a broad-spectrum senolytic activity against different types of SCs, including human IMR-90 fibroblasts, HUVECs and human renal epithelial cells (Li et al., 2019). It has been shown that EF24 induces apoptosis in various tumor cells in part by increasing ROS production and inducing oxidative stress-mediated endoplasmic reticulum stress. However, EF24 did not increase ROS production in normal or SCs, suggesting that EF24 induces apoptosis in SCs in a ROS production independent manner. Alternatively, EF24 can reduce the expression of Bcl-xl and Mcl-1 expression in SCs but not in normal cells, which may be in part mediated by the proteasomal degradation pathway. These findings provide new insights into the mechanisms by which curcumin analogs function as anti-aging agents and suggest that the curcumin analog EF24 has the potential to be used as a novel senolytic agent for the treatment of age-related diseases.

5.5 Moderate senolytic activity of goldenrod extract

In 2018, Lämmermann et al. identified an extract from the plant *Solidago virgaurea subsp. alpestris*, 1201, that can block the negative effects of senescence in human skin fibroblasts, including the SASP *in vitro* (Lämmermann et al., 2018). 1201 was not only able to delay the acquisition of a senescent phenotype, but was also able to reduce the cell numbers of SCs by 30%, with the senolytic effect of 1201 being mediated by the induction of apoptosis. Interestingly, when 1201 was added to the medium during the differentiation process of the epidermal layer, it resulted in an increase in the epidermal thickness compared to untreated controls. Thus, the natural plant extract may represent a promising possibility to block age-related loss of tissue functionality.

5.6 Effect of natural senolytics on aged mice

As summarized above, only a small number of natural compounds were evidenced to be effective senolytic agents *in vitro*. However, two of them have been demonstrated to beneficial to health in animal models, that is, fisetin and quercetin; the rest are yet to be determined. Fisetin has been shown to extend the replicative lifespan of *S. cerevisiae* by 55%

(Howitz et al., 2003) and the lifespan of *D. melanogaster* by 23% (Wood et al., 2004). Administration of fisetin to wild-type mice late in life restored tissue homeostasis, reduced age-related pathology, and extended median and maximum lifespan (Yousefzadeh et al., 2018). Given that fisetin is a natural compound found in common foods and available as an oral dietary supplement without adverse side effects, it is feasible to translate fisetin to human clinical trials in the future. For quercetin, it shows senolytic activity *in vitro* but in a cell-specific manner. The combination of quercetin with dasatinib, a tyrosine kinase receptor inhibitor, showed better effect on eliminating SCs. Single treatments of quercetin plus dasatinib had phenotypic effects persisting far after the drug is no longer present (Zhu et al., 2015). Transplanting small numbers of SCs into young mice was shown to cause persistent physical dysfunction, as well as the spread of cellular senescence to host tissues (Xu et al., 2018). The senolytic cocktail of quercetin plus dasatinib was able to cause selective elimination of SCs and decrease the number of naturally occurring SCs and SASP in explants of human adipose tissue (Xu et al., 2018). Moreover, the senolytic cocktail increased post-treatment survival by 36% while reducing mortality hazard to 65% in the study, providing proof-of-concept evidence that senolytics can enhance remaining health and lifespan in old mice (Xu et al., 2018). The existing *in vivo* results are encouraging and indicate that the natural compounds have great potential to be pushed to clinical applications (Figure 2).

6. Conclusion and Perspectives

Genetically and pharmacologically targeting fundamental mechanisms of aging is anticipated to treat or delay the onset of multiple age-related diseases (Childs et al., 2017; Hernandez-Segura et al., 2018; Kirkland and Tchkonia, 2017; Muñoz-Espín and Serrano, 2014; Naylor et al., 2013; Niedernhofer and Robbins, 2018). Cellular senescence has been demonstrated to be a key mechanism that drives aging. In this review we summarized the known senolytic agents derived from natural compounds. Natural senolytic compounds have the advantages of low toxicity, however they are usually less potent than targeted senolytics and thus have to be combined with other senolytic agents to be effective in clearing SCs (Zhu et al., 2015). Additionally, the mechanisms of action of most natural senolytics have not been well defined

nor have their molecular targets been identified and characterized, making it very difficult to rationally modify the compounds to improve their senolytic activity. Exploring and understanding the targets and mechanisms will provide insights into the mechanisms of their senolytic actions. Most of the natural compounds, except fisetin, are studied with just *in vitro* experiments; animal experiments or human population studies are urgently needed to verify their senolytic activity *in vivo*. It is promising that we develop more natural compounds to the forefront of senolytic agents and apply them in the treatment of aging and age-related diseases.

Author Contributions: Conceptualization, R.P.Z.; Writing-Original Draft Preparation, W.L., L.Q., and Y.H.H.; Writing-Review & Editing, R.P.Z.; Literature collection, R.N.F., G.R.H., and H.S.

Funding: This study was supported by grants from the National Natural Science Foundation of China (81671404), Applied Basic Research Projects of Yunnan Province (2017FA038, 2015FB003 and 2015FB006), Scientific Research Foundation of Yunnan Provincial Department of Education (2017YJS075), and the Youth Innovation Promotion Association of the Chinese Academy of Sciences (to Y.H.H.).

Conflicts of Interest: The authors declare no conflict of interest.

References

Adams, B.K., Cai, J., Armstrong, J., Herold, M., Lu, Y.J., Sun, A., Snyder, J.P., Liotta, D.C., Jones, D.P., Shoji, M., 2005. EF24, a novel synthetic curcumin analog, induces apoptosis in cancer cells via a redox-dependent mechanism. Anticancer Drugs 16, 263–275.

Aggarwal, B.B., Harikumar, K.B., 2009. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int. J. Biochem. Cell Biol. 41, 40–59.

Anand David, A.V., Arulmoli, R., Parasuraman, S., 2016. Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid. Pharmacogn Rev 10, 84–89.

Anand, P., Thomas, S.G., Kunnumakkara, A.B., Sundaram, C., Harikumar, K.B., Sung, B., Tharakan, S.T., Misra, K., Priyadarsini, I.K., Rajasekharan, K.N., Aggarwal, B.B.,

2008. Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. Biochem. Pharmacol. 76, 1590–1611.

Arai, Y., Watanabe, S., Kimira, M., Shimoi, K., Mochizuki, R., Kinae, N., 2000. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J. Nutr. 130, 2243–2250.

Assuncao, M., Andrade, J.P., 2015. Protective action of green tea catechins in neuronal mitochondria during aging. Front Biosci (Landmark Ed) 20, 247–262.

Baar, M.P., Brandt, R.M.C., Putavet, D.A., Klein, J.D.D., Derks, K.W.J., Bourgeois, B.R.M., Stryeck, S., Rijksen, Y., van Willigenburg, H., Feijtel, D.A., van der Pluijm, I., Essers, J., van Cappellen, W.A., van IJcken, W.F., Houtsmuller, A.B., Pothof, J., de Bruin, R.W.F., Madl, T., Hoeijmakers, J.H.J., Campisi, J., de Keizer, P.L.J., 2017. Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging. Cell 169, 132-147.e16.

Baker, D.J., Childs, B.G., Durik, M., Wijers, M.E., Sieben, C.J., Zhong, J., Saltness, R.A., Jeganathan, K.B., Verzosa, G.C., Pezeshki, A., Khazaie, K., Miller, J.D., van Deursen, J.M., 2016. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530, 184–189.

Baker, D.J., Wijshake, T., Tchkonia, T., LeBrasseur, N.K., Childs, B.G., van de Sluis, B., Kirkland, J.L., van Deursen, J.M., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236.

Belinha, I., Amorim, M.A., Rodrigues, P., de Freitas, V., Moradas-Ferreira, P., Mateus, N., Costa, V., 2007. Quercetin increases oxidative stress resistance and longevity in Saccharomyces cerevisiae. J. Agric. Food Chem. 55, 2446–2451.

Bent, E.H., Gilbert, L.A., Hemann, M.T., 2016. A senescence secretory switch mediated by PI3K/AKT/mTOR activation controls chemoprotective endothelial secretory responses. Genes Dev. 30, 1811–1821.

Bernatoniene, J., Kopustinskiene, D.M., 2018. The Role of Catechins in Cellular Responses to Oxidative Stress. Molecules 23.

Bezerra, D.P., Militão, G.C.G., de Castro, F.O., Pessoa, C., de Moraes, M.O., Silveira, E.R., Lima, M.A.S., Elmiro, F.J.M., Costa-Lotufo, L.V., 2007. Piplartine induces inhibition of leukemia cell proliferation triggering both apoptosis and necrosis pathways. Toxicol In Vitro 21, 1–8.

Bezerra, D.P., Pessoa, C., de Moraes, M.O., Saker-Neto, N., Silveira, E.R., Costa-Lotufo, L.V., 2013. Overview of the therapeutic potential of piplartine (piperlongumine). Eur J Pharm Sci 48, 453–463.

Boots, A.W., Haenen, G.R.M.M., Bast, A., 2008. Health effects of quercetin: from antioxidant to nutraceutical. Eur. J. Pharmacol. 585, 325–337.

Campisi, J., d'Adda di Fagagna, F., 2007. Cellular senescence: when bad things happen to good cells. Nat. Rev. Mol. Cell Biol. 8, 729–740.

Chandrashekara, K.T., Popli, S., Shakarad, M.N., 2014. Curcumin enhances parental reproductive lifespan and progeny viability in Drosophila melanogaster. Age (Dordr) 36, 9702.

Chang, J., Wang, Y., Shao, L., Laberge, R.-M., Demaria, M., Campisi, J., Janakiraman, K., Sharpless, N.E., Ding, S., Feng, W., Luo, Y., Wang, X., Aykin-Burns, N., Krager, K., Ponnappan, U., Hauer-Jensen, M., Meng, A., Zhou, D., 2016. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nat. Med. 22, 78–83.

Childs, B.G., Baker, D.J., Wijshake, T., Conover, C.A., Campisi, J., van Deursen, J.M., 2016. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science 354, 472–477.

Childs, B.G., Durik, M., Baker, D.J., van Deursen, J.M., 2015. Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat. Med. 21, 1424–1435.

Childs, B.G., Gluscevic, M., Baker, D.J., Laberge, R.-M., Marquess, D., Dananberg, J., van Deursen, J.M., 2017. Senescent cells: an emerging target for diseases of ageing. Nat Rev Drug Discov 16, 718–735.

Cormenier, J., Martin, N., Deslé, J., Salazar-Cardozo, C., Pourtier, A., Abbadie, C., Pluquet, O., 2018. The ATF6α arm of the Unfolded Protein Response mediates replicative senescence in human fibroblasts through a COX2/prostaglandin E2 intracrine pathway. Mech. Ageing Dev. 170, 82–91.

Demaria, M., Ohtani, N., Youssef, S.A., Rodier, F., Toussaint, W., Mitchell, J.R., Laberge, R.-M., Vijg, J., Van Steeg, H., Dollé, M.E.T., Hoeijmakers, J.H.J., de Bruin, A., Hara, E., Campisi, J., 2014. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev. Cell 31, 722–733.

Dinkova-Kostova, A.T., Cory, A.H., Bozak, R.E., Hicks, R.J., Cory, J.G., 2007. Bis(2-hydroxybenzylidene)acetone, a potent inducer of the phase 2 response, causes apoptosis in mouse leukemia cells through a p53-independent, caspase-mediated pathway. Cancer Lett. 245, 341–349.

Druelle, C., Drullion, C., Deslé, J., Martin, N., Saas, L., Cormenier, J., Malaquin, N., Huot, L., Slomianny, C., Bouali, F., Vercamer, C., Hot, D., Pourtier, A., Chevet, E., Abbadie, C., Pluquet, O., 2016. ATF6α regulates morphological changes associated with senescence in human fibroblasts. Oncotarget 7, 67699–67715.

Formica, J.V., Regelson, W., 1995. Review of the biology of Quercetin and related bioflavonoids. Food Chem. Toxicol. 33, 1061–1080.

Fuhrmann-Stroissnigg, H., Ling, Y.Y., Zhao, J., McGowan, S.J., Zhu, Y., Brooks, R.W., Grassi, D., Gregg, S.Q., Stripay, J.L., Dorronsoro, A., Corbo, L., Tang, P., Bukata, C., Ring, N., Giacca, M., Li, X., Tchkonia, T., Kirkland, J.L., Niedernhofer, L.J., Robbins, P.D., 2017. Identification of HSP90 inhibitors as a novel class of senolytics. Nat Commun 8, 422.

Geng, L., Liu, Z., Zhang, W., Li, W., Wu, Z., Wang, W., Ren, R., Su, Y., Wang, P., Sun, L., Ju, Z., Chan, P., Song, M., Qu, J., Liu, G.-H., 2018. Chemical screen identifies a geroprotective role of quercetin in premature aging. Protein Cell.

Grill, A.E., Shahani, K., Koniar, B., Panyam, J., 2018. Chemopreventive efficacy of curcumin-loaded PLGA microparticles in a transgenic mouse model of HER-2-positive breast cancer. Drug Deliv Transl Res 8, 329–341.

Gupta, S.C., Patchva, S., Aggarwal, B.B., 2013. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J 15, 195–218.

Harvey, A.L., 2008. Natural products in drug discovery. Drug Discov. Today 13, 894–901.

Hatcher, H., Planalp, R., Cho, J., Torti, F.M., Torti, S.V., 2008. Curcumin: from ancient medicine to current clinical trials. Cell. Mol. Life Sci. 65, 1631–1652.

Hayflick, L., Moorhead, P.S., 1961. The serial cultivation of human diploid cell strains. Exp. Cell Res. 25, 585–621.

He, S., Sharpless, N.E., 2017. Senescence in Health and Disease. Cell 169, 1000–1011.

He, Y., Li, W., Hu, G., Sun, H., Kong, Q., 2018. Bioactivities of EF24, a Novel Curcumin Analog: A Review. Front Oncol 8, 614.

He, Y., Li, W., Li, Y., Zhang, S., Wang, Y., Sun, C., 2014. Ursolic acid increases glucose uptake through the PI3K signaling pathway in adipocytes. PLoS ONE 9, e110711.

He, Y., Li, Y., Zhao, T., Wang, Y., Sun, C., 2013. Ursolic acid inhibits adipogenesis in 3T3-L1 adipocytes through LKB1/AMPK pathway. PLoS ONE 8, e70135.

Hernandez-Segura, A., Nehme, J., Demaria, M., 2018. Hallmarks of Cellular Senescence. Trends Cell Biol. 28, 436–453.

Howitz, K.T., Bitterman, K.J., Cohen, H.Y., Lamming, D.W., Lavu, S., Wood, J.G., Zipkin, R.E., Chung, P., Kisielewski, A., Zhang, L.-L., Scherer, B., Sinclair, D.A., 2003. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature 425, 191–196.

Hwang, H.V., Tran, D.T., Rebuffatti, M.N., Li, C.-S., Knowlton, A.A., 2018. Investigation of quercetin and hyperoside as senolytics in adult human endothelial cells. PLoS ONE 13, e0190374.

Jeon, O.H., Kim, C., Laberge, R.-M., Demaria, M., Rathod, S., Vasserot, A.P., Chung, J.W., Kim, D.H., Poon, Y., David, N., Baker, D.J., van Deursen, J.M., Campisi, J., Elisseeff, J.H., 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, J.N., Nambiar, A.M., Tchkonia, T., LeBrasseur, N.K., Pascual, R., Hashmi, S.K., Prata, L., Masternak, M.M., Kritchevsky, S.B., Musi, N., Kirkland, J.L., 2019. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine.

Kashyap, D., Sharma, A., Sak, K., Tuli, H.S., Buttar, H.S., Bishayee, A., 2018. Fisetin: A bioactive phytochemical with potential for cancer prevention and pharmacotherapy. Life Sci. 194, 75–87.

Khan, N., Syed, D.N., Ahmad, N., Mukhtar, H., 2013. Fisetin: a dietary antioxidant for health promotion. Antioxid. Redox Signal. 19, 151–162.

Kimira, M., Arai, Y., Shimoi, K., Watanabe, S., 1998. Japanese intake of flavonoids and isoflavonoids from foods. J Epidemiol 8, 168–175.

Kirkland, J.L., Tchkonia, T., 2017. Cellular Senescence: A Translational Perspective. EBioMedicine 21, 21–28.

Knutson, M.D., Leeuwenburgh, C., 2008. Resveratrol and novel potent activators of SIRT1: effects on aging and age-related diseases. Nutr. Rev. 66, 591–596.

Lall, R.K., Adhami, V.M., Mukhtar, H., 2016. Dietary flavonoid fisetin for cancer prevention and treatment. Mol Nutr Food Res 60, 1396–1405.

Lämmermann, I., Terlecki-Zaniewicz, L., Weinmüllner, R., Schosserer, M., Dellago, H., de Matos Branco, A.D., Autheried, D., Sevcnikar, B., Kleissl, L., Berlin, I., Morizot, F., Lejeune, F., Fuzzati, N., Forestier, S., Toribio, A., Tromeur, A., Weinberg, L., Higareda Almaraz, J.C., 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.

Li, T., Chen, S., Feng, T., Dong, J., Li, Y., Li, H., 2016. Rutin protects against aging-related metabolic dysfunction. Food Funct 7, 1147–1154.

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.

Liao, V.H.-C., Yu, C.-W., Chu, Y.-J., Li, W.-H., Hsieh, Y.-C., Wang, T.-T., 2011. Curcumin-mediated lifespan extension in Caenorhabditis elegans. Mech. Ageing Dev. 132, 480–487.

Liu, X., Lin, X., Mi, Y., Li, J., Zhang, C., 2018. Grape Seed Proanthocyanidin Extract Prevents Ovarian Aging by Inhibiting Oxidative Stress in the Hens. Oxid Med Cell Longev 2018, 9390810.

López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.

Maheshwari, R.K., Singh, A.K., Gaddipati, J., Srimal, R.C., 2006. Multiple biological activities of curcumin: a short review. Life Sci. 78, 2081–2087.

Marković, Z.S., Mentus, S.V., Dimitrić Marković, J.M., 2009. Electrochemical and density functional theory study on the reactivity of fisetin and its radicals: implications on in vitro antioxidant activity. J Phys Chem A 113, 14170–14179.

Molinski, T.F., Dalisay, D.S., Lievens, S.L., Saludes, J.P., 2009. Drug development from marine natural products. Nat Rev Drug Discov 8, 69–85.

Mukherjee, P.K., Maity, N., Nema, N.K., Sarkar, B.K., 2011. Bioactive compounds from natural resources against skin aging. Phytomedicine 19, 64–73.

Muñoz-Espín, D., Rovira, M., Galiana, I., Giménez, C., Lozano-Torres, B., Paez-Ribes, M., Llanos, S., Chaib, S., Muñoz-Martín, M., Ucero, A.C., Garaulet, G., Mulero, F., Dann, S.G., VanArsdale, T., Shields, D.J., Bernardos, A., Murguía, J.R., Martínez-Máñez, R., Serrano, M., 2018. A versatile drug delivery system targeting senescent cells. EMBO Mol Med 10.

Muñoz-Espín, D., Serrano, M., 2014. Cellular senescence: from physiology to pathology. Nat. Rev. Mol. Cell Biol. 15, 482–496.

Naylor, R.M., Baker, D.J., van Deursen, J.M., 2013. Senescent cells: a novel therapeutic target for aging and age-related diseases. Clin. Pharmacol. Ther. 93, 105–116.

Newman, D.J., Cragg, G.M., 2016. Natural Products as Sources of New Drugs from 1981 to 2014. J. Nat. Prod. 79, 629–661.

Niedernhofer, L.J., Robbins, P.D., 2018. Senotherapeutics for healthy ageing. Nat Rev Drug Discov 17, 377.

Pal, H.C., Pearlman, R.L., Afaq, F., 2016. Fisetin and Its Role in Chronic Diseases. Adv. Exp. Med. Biol. 928, 213–244.

Piska, K., Gunia-Krzyżak, A., Koczurkiewicz, P., Wójcik-Pszczoła, K., Pękala, E., 2018. Piperlongumine (piplartine) as a lead compound for anticancer agents - Synthesis and properties of analogues: A mini-review. Eur J Med Chem 156, 13–20.

Sastre, J., Millán, A., García de la Asunción, J., Plá, R., Juan, G., Pallardó, null, O'Connor, E., Martin, J.A., Droy-Lefaix, M.T., Viña, J., 1998. A Ginkgo biloba extract (EGb 761) prevents mitochondrial aging by protecting against oxidative stress. Free Radic. Biol. Med. 24, 298–304.

Selvendiran, K., Kuppusamy, M.L., Bratasz, A., Tong, L., Rivera, B.K., Rink, C., Sen, C.K., Kálai, T., Hideg, K., Kuppusamy, P., 2009. Inhibition of vascular smooth-muscle cell proliferation and arterial restenosis by HO-3867, a novel synthetic curcuminoid, through up-regulation of PTEN expression. J. Pharmacol. Exp. Ther. 329, 959–966.

Sharpless, N.E., Sherr, C.J., 2015. Forging a signature of in vivo senescence. Nat. Rev. Cancer 15, 397–408.

Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., Srinivas, P.S., 1998. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 64, 353–356.

Singh, A., Naidu, P.S., Kulkarni, S.K., 2003. Reversal of aging and chronic ethanol-induced cognitive dysfunction by quercetin a bioflavonoid. Free Radic. Res. 37, 1245–1252.

Sundarraj, K., Raghunath, A., Perumal, E., 2018. A review on the chemotherapeutic potential of fisetin: In vitro evidences. Biomed. Pharmacother. 97, 928–940.

Takano, K., Tatebe, J., Washizawa, N., Morita, T., 2018. Curcumin Inhibits Age-Related Vascular Changes in Aged Mice Fed a High-Fat Diet. Nutrients 10.

Tamvakopoulos, C., Dimas, K., Sofianos, Z.D., Hatziantoniou, S., Han, Z., Liu, Z.-L., Wyche, J.H., Pantazis, P., 2007. Metabolism and anticancer activity of the curcumin analogue, dimethoxycurcumin. Clin. Cancer Res. 13, 1269–1277.

Wang, W., Sun, C., Mao, L., Ma, P., Liu, F., Yang, J., Gao, Y., 2016. The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review. Trends in Food Science & Technology 56, 21–38.

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

Wood, J.G., Rogina, B., Lavu, S., Howitz, K., Helfand, S.L., Tatar, M., Sinclair, D., 2004. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature 430, 686–689.

Xu, M., Pirtskhalava, T., Farr, J.N., Weigand, B.M., Palmer, A.K., Weivoda, M.M., Inman, C.L., Ogrodnik, M.B., Hachfeld, C.M., Fraser, D.G., Onken, J.L., Johnson, K.O., Verzosa, G.C., Langhi, L.G.P., Weigl, M., Giorgadze, N., LeBrasseur, N.K., Miller, J.D., Jurk, D., Singh, R.J., Allison, D.B., Ejima, K., Hubbard, G.B., Ikeno, Y., Cubro, H., Garovic, V.D., Hou, X., Weroha, S.J., Robbins, P.D., Niedernhofer, L.J., Khosla, S., Tchkonia, T., Kirkland, J.L., 2018. Senolytics improve physical function and increase lifespan in old age. Nat. Med. 24, 1246–1256.

Xu, Z., Feng, W., Shen, Q., Yu, N., Yu, K., Wang, S., Chen, Z., Shioda, S., Guo, Y., 2017. Rhizoma Coptidis and Berberine as a Natural Drug to Combat Aging and Aging-Related Diseases via Anti-Oxidation and AMPK Activation. Aging Dis 8, 760–777.

Yang, L., Zheng, Z., Qian, C., Wu, J., Liu, Y., Guo, S., Li, G., Liu, M., Wang, X., Kaplan, D.L., 2017. Curcumin-functionalized silk biomaterials for anti-aging utility. J Colloid Interface Sci 496, 66–77.

Yang, Y.-C., Lin, H.-Y., Su, K.-Y., Chen, C.-H., Yu, Y.-L., Lin, C.-C., Yu, S.-L., Yan, H.-Y., Su, K.-J., Chen, Y.-L.S., 2012. Rutin, a Flavonoid That Is a Main Component of Saussurea involucrata, Attenuates the Senescence Effect in D-Galactose Aging Mouse Model. Evid Based Complement Alternat Med 2012, 980276.

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.

Yousefzadeh, M.J., Zhu, Y., McGowan, S.J., Angelini, L., Fuhrmann-Stroissnigg, H., Xu, M., Ling, Y.Y., Melos, K.I., Pirtskhalava, T., Inman, C.L., McGuckian, C., Wade, E.A., Kato, J.I., Grassi, D., Wentworth, M., Burd, C.E., Arriaga, E.A., Ladiges, W.L., Tchkonia, T., Kirkland, J.L., Robbins, P.D., Niedernhofer, L.J., 2018. Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine 36, 18–28.

Zhang, Xin, Zhang, S., Liu, X., Wang, Y., Chang, J., Zhang, Xuan, Mackintosh, S.G., Tackett, A.J., He, Y., Lv, D., 2018. Oxidation resistance 1 is a novel senolytic target. Aging cell e12780.

Zhu, Y., Doornebal, E.J., Pirtskhalava, T., Giorgadze, N., Wentworth, M., Fuhrmann-Stroissnigg, H., Niedernhofer, L.J., Robbins, P.D., Tchkonia, T., Kirkland, J.L., 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, H.M., Ling, Y.Y., Stout, M.B., Pirtskhalava, T., Giorgadze, N., Johnson, K.O., Giles, C.B., Wren, J.D., Niedernhofer, L.J., Robbins, P.D., Kirkland, J.L., 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, A.C., Ding, H., Giorgadze, N., Palmer, A.K., Ikeno, Y., Hubbard, G.B., Lenburg, M., O'Hara, S.P., LaRusso, N.F., Miller, J.D., Roos, C.M., Verzosa, G.C., LeBrasseur, N.K., Wren, J.D., Farr, J.N., Khosla, S., Stout, M.B., McGowan, S.J., Fuhrmann-Stroissnigg, H., Gurkar, A.U., Zhao, J., Colangelo, D., Dorronsoro, A., Ling, Y.Y., Barghouthy, A.S., Navarro, D.C., Sano, T., Robbins, P.D., Niedernhofer, L.J., Kirkland, J.L., 2015. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell 14, 644–658.

Figure legends

Figure 1. Cellular senescence and senolytics. Senescence-induced stimuli lead to normal cells to be senescent, senolytic agents can eliminate senescent cells (SCs) and promote regeneration of normal cells.

Figure 2. Benefits of natural senolytics on aging. During the aging process, senescent cells (SCs) accumulate in tissues and associated with various age-related diseases. Senolytics derived from nature plants may help delay aging, reduce age-related diseases and extend healthspan through eliminating SCs.

Figures

Figure 1.

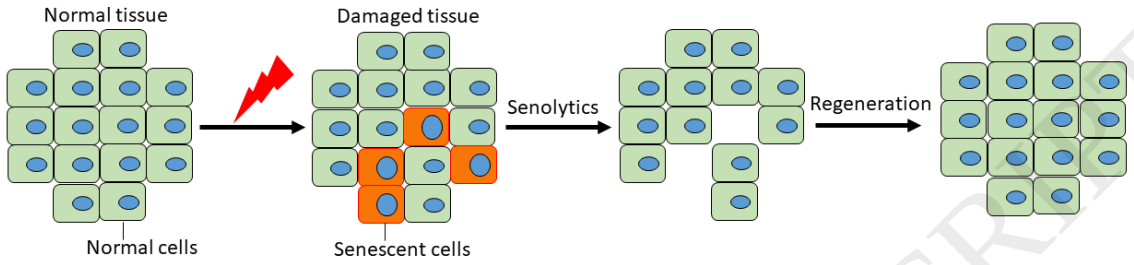

Figure 2.