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MINIREVIEWS

Emerging use of senolytics and senomorphics against aging and chronic diseases

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Abstract

Senescence is a state of cell cycle arrest that plays an important role in embryogenesis, wound healing and protection against cancer. Senescent cells also accumulate during aging and contribute to the development of age-related disorders and chronic diseases, such as atherosclerosis, type 2 diabetes, osteoarthritis, idiopathic pulmonary fibrosis, and liver disease. Molecules that induce apoptosis of senescent cells, such as dasatinib, quercetin, and fisetin, produce health benefits and extend lifespan in animal models. We describe here the mechanism of action of senolytics and senomorphics, many of which are derived from plants and fungi. We also discuss the possibility of using such compounds to delay aging and treat chronic diseases in humans.

KEYWORDS

aging, apoptosis, dietary supplements, phytochemicals, senescence

1 | INTRODUCTION

Aging is a highly malleable process that can be modulated in different ways. One of the most studied antiaging interventions is caloric restriction (CR), which prolongs lifespan in a variety of living organisms, including yeast, nematodes, fruit flies, and monkeys.[1] Other antiaging interventions include intermittent fasting,[2,3] exercise[4,5] and a plant-based diet rich in phytochemicals.[6,7] These interventions may delay aging and improve longevity by activating stress resistance and repair mechanisms that include autophagy, mitochondrial biogenesis, DNA repair, and expression of antioxidant and detoxifying enzymes.[1,7-9] Notably, CR, intermittent fasting, exercise and phytochemicals extend lifespan but also reduce the development of chronic diseases, therefore improving both health and longevity.

Cellular senescence—a state of cell cycle arrest described over 50 years ago in cultured cells[10]—is one of the hallmarks of aging. Cells maintained in culture undergo a finite number of divisions before entering senescence due mainly to telomere erosion.[11] More recent studies have shown that senescent cells are metabolically active and play a major role in tissue homeostasis.[12] For instance, senescent cells that form during embryogenesis contribute to cell fate specification and tissue patterning.[13] In the adult body, senescent cells are involved in wound healing via the release of growth factors[14] and cytokines that may initially activate resident stem cells (Figure 1).[12,15] The senescence-associated secretory phenotype (SASP) also includes proinflammatory cytokines that attract immune cells to the site of injury, leading to removal of senescent cells by phagocytosis to restore homeostasis (Figure 1).[16]

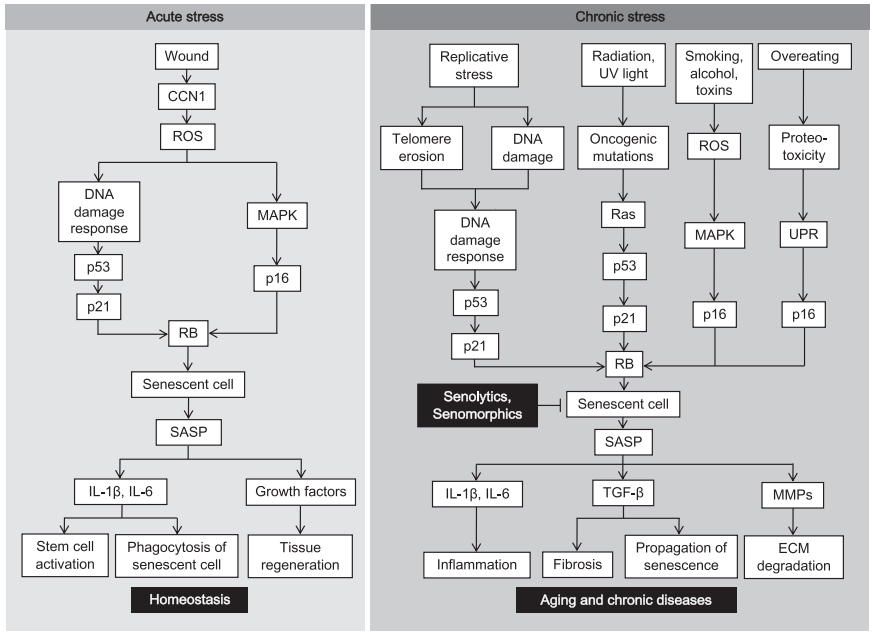

FIGURE 1 Role of senescence in maintenance of tissue homeostasis and aging. Senescence plays critical roles in response to acute stress by inducing tissue repair and regeneration. In contrast, senescence induced by chronic stress is involved in aging and disease progression. Senolytics and senomorphics target senescence, producing health benefits against aging and chronic diseases. Chronic stress may result from either intrinsic stimuli (eg, telomere erosion, aberrant DNA replication) or extrinsic stimuli (eg, excess sunlight, smoking, alcohol, and toxins). CCN1, cellular communication network factor-1; ECM, extracellular matrix; IL, interleukin; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; RB, retinoblastoma protein; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; TGF-β, transforming growth factor-β; UPR, unfolded protein response

Cells that sustain DNA damage activate the tumor suppressors p16, p21, and p53 and stop replicating, a process that prevents cancer development.[17]

While senescence is beneficial during embryogenesis and to maintain tissue homeostasis, chronic stress may lead to accumulation of senescent cells in aging and diseased tissues (Figure 1). Senescent cells contribute to tissue dysfunction due to the SASP, which includes factors that induce inflammation (eg, interleukin [IL]-1β and IL-6), extracellular matrix degradation (eg, matrix metalloproteinases), as well as fibrosis and secondary senescence in neighboring cells (eg, via IL-1β and transforming growth factor-β [TGF-β]).[16] Senescence also occurs in stem cells, limiting tissue repair and regeneration.[18] Moreover, chronic stress increases the number of senescent cells in various tissues, contributing to the development of diseases, such as atherosclerosis, type 2 diabetes, osteoarthritis, idiopathic pulmonary fibrosis, and liver disease.[16] Senescence is thus beneficial when activated in damaged cells exposed to acute stress, but it is detrimental in aging and chronic diseases when induced by chronic stress (Figure 1).

The use of bioactive compounds to eliminate senescent cells has recently emerged as a promising approach to delay aging and reduce the severity of chronic diseases. Many synthetic and plant-derived molecules induce apoptosis of senescent cells[12,19,20]; we review here their mechanism of action and the possibility of using these compounds to improve health and longevity.

2 | IDENTIFICATION OF SENOLYTICS TO DELAY AGING

Senescent cells accumulate in aging tissues in mice[21] and humans[22] due to telomere erosion and DNA damage. Accordingly, signs of the DNA damage response induced by telomere erosion accumulate in a time-dependent manner in the liver and gut of mice.[23] Markers of senescence, such as *p16* expression and senescence-associated β-galactosidase (SA-β-Gal), increase in tissues of aged mice.[24] While senescent cells may represent only 1% to 15% of the total cell population in any given tissue,[17] they are believed to negatively affect tissue function due to SASP factors, stem cell loss, and impaired clearance by the aging immune system.[16] In one study, transplanting senescent preadipocytes into mice so that the senescent cells represented only 0.007% of the recipient's cells was sufficient to reduce maximal walking speed, hanging time and grip strength.[25]

The first indications that senescent cells may contribute to aging were obtained from studies performed on transgenic mice. The removal of *p16*-positive senescent cells using a transgenic suicide gene in a mouse model of premature (progeroid) aging reduced the development of aging-related disorders, such as sarcopenia, lipodystrophy, hunchback and cataracts.[26] Elimination of naturally-occurring senescent *p16*-positive cells in wild-type mice also extended lifespan and produced beneficial effects in the kidneys, heart, and fat tissues.[27] Another study showed that transgenic mice lacking perforin—a pore-forming protein that we showed earlier can mediate targeted cell killing by lymphocytes[28,29]—present signs of premature aging and lower survival due to accumulation of senescent cells in various tissues,[30] confirming that immunosurveillance is needed to eliminate senescent cells from the body.

An early study that identified "senolytic" compounds able to kill senescent cells used bioinformatics to assess the antiapoptotic signaling pathways that maintain the senescence phenotype.[31] These senescent cell antiapoptotic pathways (SCAPs) include the Bcl-2 protein family, phosphoinositide 3-kinase (PI3K), Akt, p53, p21, serpins, ephrins, tyrosine kinases, hypoxia-inducible factor-1α, and heat-shock protein 90 (HSP90). Based on this analysis, quercetin [**1**], a plant flavonoid found in many fruits, vegetables and grains, was selected for its ability to inhibit PI3K and Akt in senescent cells[31] (Figures 2 and 3; Table 1). Quercetin induced apoptosis in human senescent endothelial cells to a greater extent than in proliferating endothelial cells.[31] However, quercetin was less effective at inducing apoptosis of human senescent preadipocytes, indicating that senolytics produce cell type-specific effects that depend on the specific SCAPs expressed in each cell population[32] (Figure 2). To address this issue, quercetin was combined with dasatinib [**2**], a nonspecific tyrosine kinase inhibitor that interferes with ephrin-

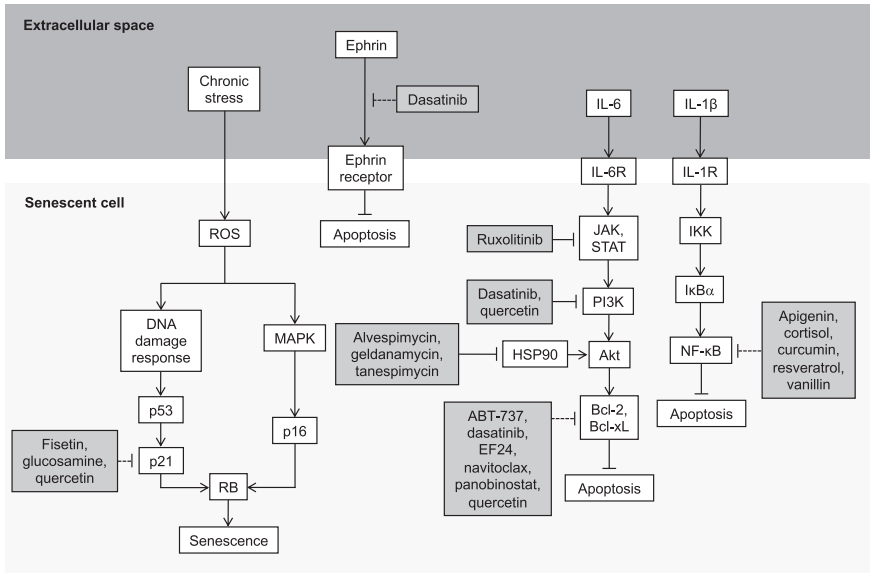

FIGURE 2 Model illustrating the effects of bioactive molecules on senescence. Various cellular pathways maintain the phenotype of senescent cells, including activation of the tumor suppressors p16 and p53. Other cellular pathways inhibit apoptosis in senescent cells, including those activated by ephrin ligands and proinflammatory cytokines, such as IL-1β and IL-6. Senolytic molecules induce apoptosis by inhibiting pro-senescence pathways or by inhibiting antiapoptotic signaling, in a direct or indirect manner. Bcl, B-cell lymphoma; HSP90, heat-shock protein 90; IKK, inhibitor of nuclear factor kappa B kinase; IκBα, inhibitor of nuclear factor kappa B kinase subunit alpha; IL-1R, interleukin-1 receptor; IL-6R, interleukin-6 receptor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; RB, retinoblastoma protein; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription

dependent inhibition of apoptosis in cancer cells.[33] In vitro, dasatinib can kill human senescent preadipocytes.[31] When tested in mice, the cocktail of quercetin and dasatinib not only reduced the number of senescent cells but also delayed aging as revealed by improved cardiac function and exercise capacity.[31] Intermittent treatment with the senolytic cocktail reduced frailty and extended median lifespan by 36%.[25]

Further studies showed that the anticancer compound navitoclax [**3**], an inhibitor of antiapoptotic Bcl-2 proteins, possesses senolytic properties in some but not all cell types in vitro. As such, navitoclax reduced the viability of human senescent umbilical vein epithelial cells (HUVECs), human lung fibroblasts and murine embryonic fibroblasts but not human senescent preadipocytes.[34] Navitoclax also reduced the number of senescent bone marrow hematopoietic stem cells and senescent muscle stem cells in aged and sub-lethally irradiated mice.[35] Similarly, ABT-737 [**4**], an inhibitor of antiapoptotic Bcl-xL and Bcl-W proteins, reduced the senescent cell burden in the lungs and epidermis of mice, increasing hair-follicle stem cell proliferation.[36] However, ABT-737 showed poor bioavailability in humans while navitoclax produced thrombocytopenia, which may limit the use of these compounds in humans.[37] Other Bcl-2 inhibitors, such as A-1331852 [**5**] and A-1155463 [**6**], were also senolytic in senescent HUVECs and human lung fibroblasts,[38] while venetoclax was less potent.[39] A small 46-amino-acid peptide referred to as FOXO4-DRI, which disrupts the interaction between FOXO4 and the proapoptotic protein p53, also induced apoptosis in human senescent lung fibroblasts.[40] Treatment with this peptide restored fitness, fur density and renal function in aged mice.

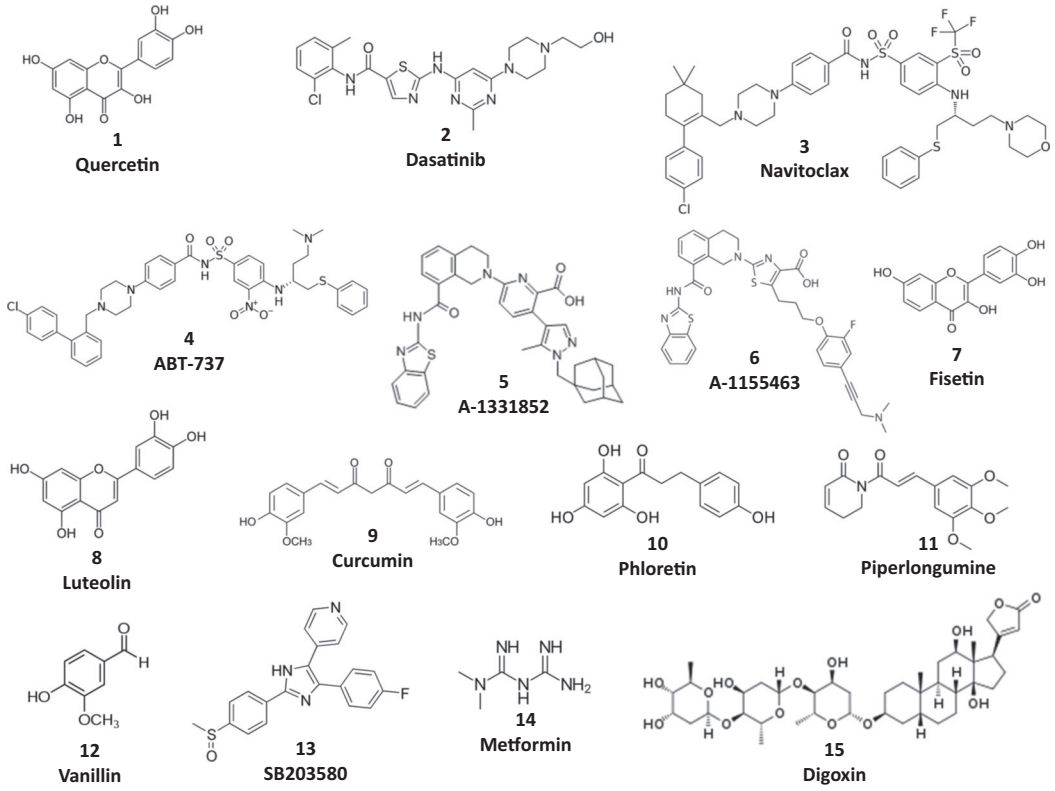

FIGURE 3 Chemical structures of senolytics and senomorphics

Many phytochemicals have been screened for their ability to inhibit senescence.[41] In a panel of 10 polyphenols examined, fisetin [**7**] was the most potent senolytic in cultured senescent murine and human fibroblasts; luteolin [**8**] and curcumin [**9**] produced weak effects in these experiments. When tested in aged wild-type mice, fisetin reduced senescent cell accumulation in various tissues as well as pathological scores in the brain and liver. Notably, fisetin increased median and maximum lifespan when given to aged mice.[41] Fisetin treatment could thus extend lifespan even when initiated late in life, suggesting that this treatment could be highly beneficial if the results can be reproduced in humans. Other phytochemicals that possess senolytic activity include phloretin [**10**], piperlongumine [**11**] and vanillin [**12**] (Table 1).

In addition to synthetic compounds possessing anti-inflammatory activity (SB203580 [**13**]), many pharmaceutical drugs already used in humans have been shown to target senescence (Table 1). These include antidiabetic drugs (metformin [**14**]), cardiac glycosides (digoxin [**15**]), lipid-lowering drugs (simvastatin [**16**]), histone deacetylase inhibitors (panobinostat [**17**]), anticancer compounds (dasatinib, navitoclax, ruxolitinib [**18**]), immunosuppressive drugs (cortisol [**19**]) and antibiotics (azithromycin [**20**], roxithromycin [**21**]). These molecules target senescent cells by affecting pro-senescence or antiapoptotic effectors including PI3K, Akt, Bcl-2 protein family, p21, p53, Nrf2, and NF-κB[31,42] (Table 1 and Figure 2). Notably, small anticancer compounds, such as alvespimycin [**22**], geldanamycin [**23**] and tanespimycin [**24**], also produced senolytic activity by inhibiting HSP90.[43] Alvespimycin delayed age-related symptoms in progeroid *Ercc1*$^{-/\Delta}$ mice.[43] HSP90 inhibitors may induce senolytic activity by preventing interactions between HSP90 and its client protein, phosphorylated Akt, which possesses antiapoptotic activity.[43]

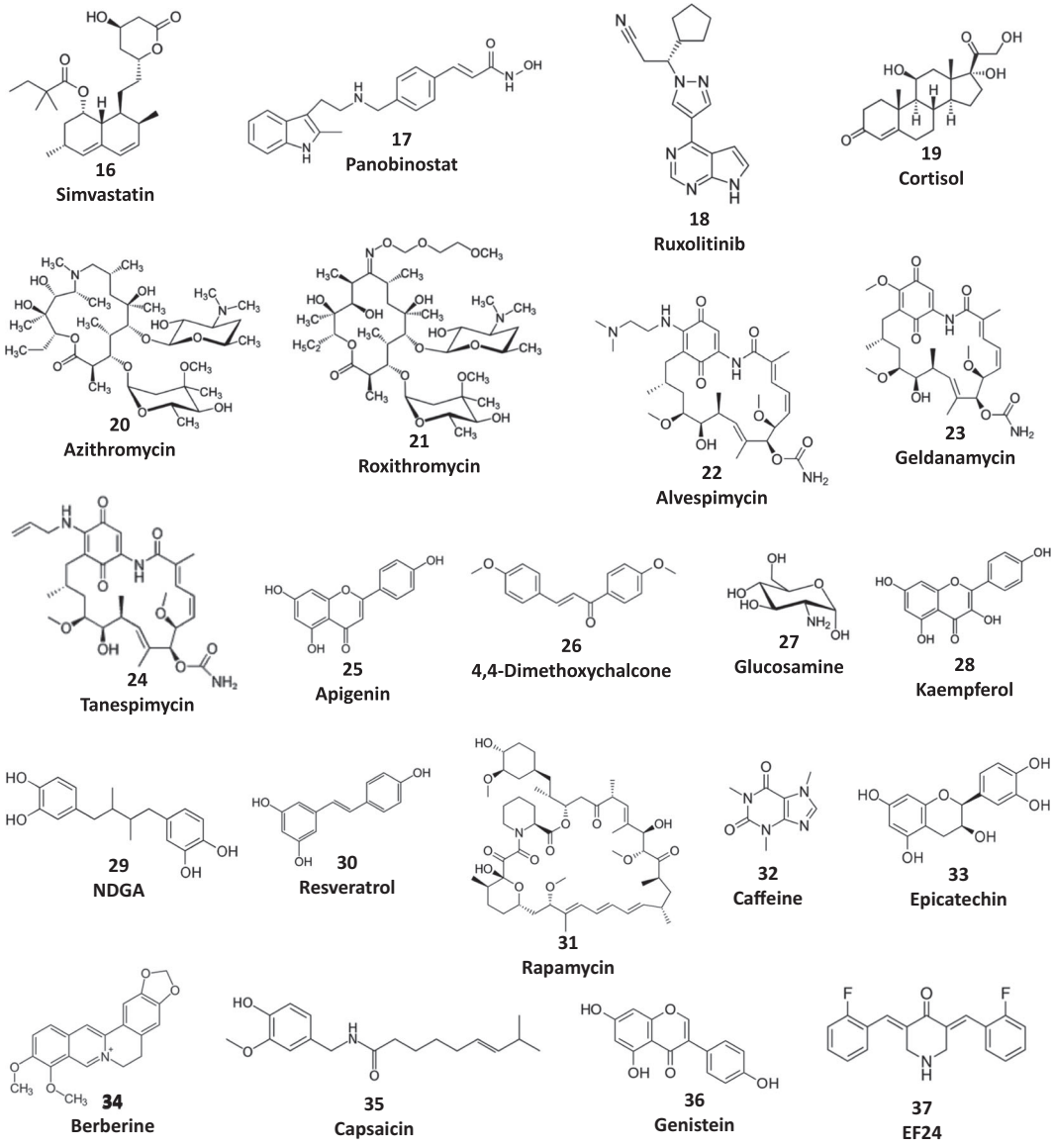

FIGURE 3 (Continued)

It is important to note that, in addition to targeting senescence, phytochemicals and pharmaceutical drugs may interact with other molecular targets and produce additional bioactivities that contribute to their health benefits. For instance, phytochemicals and fungal compounds can improve the composition of the gut microbiota and modulate antiaging pathways in mammalian cells.[7,9,44,45] Quercetin interacts with cyclooxygenases, lipoxygenases, mitogen-activated protein kinases and matrix metalloproteinases, producing anti-inflammatory and anticancer effects.[46] In addition to senescence, it is therefore likely that these senolytics may produce health benefits by targeting other aging-related pathways.

TABLE 1 Compounds that produce senolytic or senomorphic activity

Compound	Source	Mechanism	Biological activity	References
A-1155463	Synthetic	↓Bcl-xL	↓Senescent HUVECs and senescent human lung fibroblasts in vitro	Zhu et al[38]
A-1331852	Synthetic	↓Bcl-xL	↓Senescent HUVECs and senescent human lung fibroblasts in vitro	Zhu et al[38]
ABT-737	Synthetic	↓Bcl-xL, ↓Bcl-W, ↑apoptosis	↓Senescent cells in lungs and epidermis of mice; ↑hair-follicle stem cell proliferation in mice	Yosef et al[36]
Alvespimycin	Synthetic (geldanamycin derivative)	↓HSP90	↓Senescent murine embryonic fibroblasts in vitro; ↓Age-related symptoms in progeroid *Ercc1*$^{-/\Delta}$ mice	Fuhrmann-Stroissnigg et al[43]
Apigenin	Plants, fruits, vegetables, tea	↓NF-κB	↓SASP in fibroblasts; ↓SASP in kidneys of aged rats	Lim et al[92]
Azithromycin	Drug	↑Autophagy	↓Viability of human senescent lung and skin fibroblasts	Ozsvari et al[93]
Cardiac glycosides	Plants (foxglove)	↓Na^+/K^+ ATPase, ↑apoptosis	↓Human senescent lung adenocarcinoma A549 cells, primary fibroblasts and osteoarthritic chondrocytes in vitro; ↓enhanced the effects of chemotherapy against tumor xenografts in mice; ↓senescent cells and fibrosis in a mouse model of lung fibrosis	Triana-Martinez et al[94]
Cortisol (+corticosterone)	Hormone, drug	↓NF-κB	↓SASP in human fibroblasts in vitro	Laberge et al[95]
Curcumin (+analogs)	Turmeric, dietary supplement	↓Nrf2, ↓NF-κB, ↑apoptosis	↓Senescent human IVD cells and ↓SASP ex vivo; showed weak or no senolytic activity in senescent *Ercc1*$^{-/-}$ murine embryonic fibroblasts	Yousefzadeh et al,[41] Fuhrmann-Stroissnigg et al,[43] Cherif et al[96]
4,4′-Dimethoxychalcone	*Angelica keiskei koidzumi* (plant)	↑Autophagy	↓Senescence-mediated clonogenic survival in human cancer cells in vitro; ↓myocardial ischemia in mice	Carmona-Gutierrez et al[97]

(Continues)

TABLE 1 (Continued)

Compound	Source	Mechanism	Biological activity	References
EF24	Curcumin analog	↓Bcl-2, ↑apoptosis	↓Viability of human senescent fibroblasts	Li et al[82]
Fisetin	Plants, fruits, dietary supplement	↓p16, ↓p21, ↑cleaved caspase-3/7, ↑apoptosis	↓Senescent human cells in vitro; ↓senescent cells and ↓SASP in progeroid and aged mice in vivo; ↓age-related pathology and ↑lifespan of wild-type, aged mice	Yousefzadeh et al,[41] Zhu et al[38]
FOXO4-DRI peptide	Synthetic	↑p53, ↑apoptosis	↑Apoptosis of human senescent lung fibroblasts; ↑fitness, ↑fur density and ↑renal functions in aged $Xpd^{TTD/TTD}$ and wild-type mice	Baar et al[40]
Geldanamycin	*Streptomyces hygroscopicus*, drug	↓HSP90	↓Senescent murine embryonic fibroblasts in vitro	Fuhrmann-Stroissnigg et al[43]
Glucosamine	Dietary supplement	↓ROS, ↓p21, ↑autophagy	↓Senescence of rat nucleus pulposus cells and human retinal pigment epithelial cells in vitro	Jiang et al,[98] Chen et al[99]
Kaempferol	Plants, fruits, vegetables	↓NF-κB	↓SASP in fibroblasts	Lim et al[92]
Luteolin	Plants, tea, spices	Not determined	Weak senolytic activity in senescent *Ercc1*$^{-/-}$ murine embryonic fibroblasts	Yousefzadeh et al[41]
Metformin	Drug (derived from French lilac)	↓NF-κB, ↑DICER1, ↓Akt, ↓p16, ↓p21	↓SASP in human senescent lung fibroblasts in vitro; ↓ceramide-induced senescence in myoblasts in vitro; ↓human senescent lung fibroblasts in vitro	Moisseva et al,[100] Jadhav et al,[101] Noren Hooten et al[102]
Mixture	*Hirsutella sinensis* mycelium, dietary supplement	↓Akt, ↓ROS, ↓IL-1β, ↓collagen, ↓TGF-β	↓Bleomycin-induced fibrosis and lung injury in mice	Huang et al[56]
Mixture	*Solidago virgaurea* (plant)	Not determined	↓Senescence and ↓SASP in human dermal fibroblasts in vitro	Lammermann et al[103]
Navitoclax	Drug	↓Bcl-2	↓Viability of senescent HUVECs, human lung fibroblasts and murine embryonic fibroblasts; ↓senescent hematopoietic stem cells and muscle stem cells in aged and irradiated mice	Zhu et al,[34] Chang et al[35]

TABLE 1 (Continued)

Compound	Source	Mechanism	Biological activity	References
Nordihydroguaiaretic acid	Creosote bush	Not determined	↓Senescence in murine embryonic fibroblasts in vitro	Fuhrmann-Stroissnigg et al[43]
Panobinostat	Drug	↓Bcl-xL	↓Viability of senescent lung cancer cells in vitro	Samaraweera et al[104]
Phloretin (chalcone)	Plants, fruits	↓Glucose uptake, ↑apoptosis	↓Senescent cell viability in vitro	Dorr et al[105]
Piperlongumine (+analogs)	Piper plants	↑Caspase-3, ↑apoptosis	↓Senescent human cell viability in vitro	Wang et al[83]
Quercetin +dasatinib	Vegetables, dietary supplement, drug	↓Bcl-xL, ↓PI3K/Akt, ↓p16, ↓p21, ↑cleaved caspase-3, ↑apoptosis	↓Senescent human cells in vitro; ↑vasomotor function in aged and hypercholesterolemic mice; ↑exercise capacity and ↓SASP in mice; ↓hepatic steatosis in mice; ↑lifespan of progeroid and wild-type mice; ↓Alzheimer's disease in mice; ↓insulin resistance in obese mice; ↓physical dysfunction in human IPF patients; ↓anxiety in obese mice; ↑renal function in obese mice	Zhu et al,[31] Fuhrmann-Stroissnigg et al,[43] Palmer et al,[50] Ogrodnik et al,[51] Roos et al,[52] Zhang et al,[53] Ogrodnik et al,[54] Kim et al,[55] Justice et al,[75] Xu et al,[25] Hickson et al[76]
Rapamycin	*S. hygroscopicus*, drug	↓mTOR, ↓p16, ↓p21, ↑autophagy, ↓ROS, ↓NF-κB	↓p16/p21-induced senescence in rodent and human cells in vitro; ↓senescence in progeroid human fibroblasts ex vivo; ↓senescence in human primary keratinocytes and epithelial stem cells in vitro; ↓radiation-induced mucositis in mice; ↓SASP in human fibroblasts and breast epithelial cells in vitro; ↓senescence and SASP in mouse fibroblasts in vitro; ↓SASP and senescent cells in serum and fat tissues of mice; ↓number of senescent *Ercc1*$^{-/-}$ murine embryonic fibroblasts in vitro	Demidenko et al,[106] Cao et al,[107] Iglesias-Bartolome et al,[108] Laberge et al,[69] Wang et al,[109] Fuhrmann-Stroissnigg et al[43]
Resveratrol	Fruits, red wine, dietary supplement	↑SIRT-1	↓Senescence of human cells in vitro; ↑learning and memory in senescence-accelerated mice; no effect on senescent *Ercc1*$^{-/-}$murine embryonic fibroblasts in vitro	Kao et al,[59] Zhang et al,[60] Liu et al,[110] Fuhrmann-Stroissnigg et al,[43] Lei et al[111]

(Continues)

TABLE 1 (Continued)

Compound	Source	Mechanism	Biological activity	References
Roxithromycin	Drug	↑Autophagy	↓Viability of human senescent lung and skin fibroblasts	Ozsvari et al[93]
Ruxolitinib	Drug	↓JAK	↓SASP in human primary preadipocytes and HUVECs in vitro; ↓inflammation and ↑physical function in aged mice	Xu et al[112]
SB203580	Synthetic	↓p38 MAPK	↓SASP in human fibroblasts in vitro	Freund et al[113]
Simvastatin	Drug (derived from *Aspergillus terreus*)	↓Protein prenylation, ↓Rho GTPase	↓SASP in human fibroblasts in vitro	Liu et al[114]
Tanespimycin	Synthetic (geldanamycin derivative)	↓HSP90	↓Senescent murine embryonic fibroblasts in vitro	Fuhrmann-Stroissnigg et al[43]
Vanillin	Vanilla beans	↓Nrf2, ↓NF-κB, ↑apoptosis	↓Senescent IVD cells; ↓SASP	Cherif et al[96]

Abbreviations: Bcl, B-cell lymphoma; HSP90, heat-shock protein 90; HUVECs, human umbilical vein epithelial cells; IL-1β, interleukin-1β; IPF, idiopathic pulmonary fibrosis; IVD, intervertebral disc; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor (erythroid-derived 2)-related factor 2; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SIRT-1, sirtuin-1; TGF-β, transforming growth factor-β.

3 | EFFECTS OF SENOLYTICS AGAINST CHRONIC DISEASES

Senescent cells accumulate in organs in various animal models of chronic disease. For instance, mice fed a high-fat diet for 12 months showed signs of senescence in pancreatic β-cells and adipocytes, which was associated with insulin resistance.[47] Apolipoprotein E-deficient mice fed a HFD also presented signs of senescent endothelial cells in blood vessels, eventually leading to atherosclerosis.[48] Similarly, mice fed ad libitum or treated with liver-damaging agents, such as alcohol or carbon tetrachloride showed increased senescent cells in the liver as well as signs of fibrosis, steatosis and liver disease.[49]

In model organisms, senolytics derived from plants reduced aging-related chronic diseases (Table 1). The senolytic cocktail of quercetin and dasatinib reduced senescent cells in adipose tissues of obese mice, which was associated with reduced inflammation and improved insulin resistance and cardiac function.[50] Similarly, the senolytic cocktail reduced the accumulation of senescent hepatocytes and the severity of liver steatosis in aged and diabetic mice.[51] Intermittent treatment with quercetin and dasatinib also reduced aortic calcification and markers of senescence in arteries of aged and hypercholesterolemic mice.[52] Another study showed that treatment with quercetin and dasatinib alleviated neurodegeneration in a mouse model of Alzheimer's disease.[53] The quercetin-dasatinib cocktail also restored neurogenesis and reduced anxiety in HFD-fed and transgenic obese mice.[54] Treatment with quercetin reduced senescence markers and improved kidney functions in HFD-fed mice,[55] indicating that the plant-derived compound can produce senolytic effects even when used alone.

We observed earlier that an ethanol extract of the medicinal fungus *Hirsutella sinensis* reduced bleomycin-induced lung injury and fibrosis in mice.[56] The mycelium extract reduced levels of TGF-β and IL-1β,[56] two SASP cytokines that can induce secondary senescence in neighboring cells.[16] Similarly, a previous study showed that the cocktail of quercetin and dasatinib reduced senescent cell burden and lung fibrosis in bleomycin-treated mice.[57] In addition, polysaccharides derived from the medicinal fungi *Ganoderma lucidum* and *H. sinensis* reduced body weight, inflammation and insulin resistance in a model of HFD-fed mice.[44,58] Notably, the polysaccharides reduced the formation of crown-like structures consisting of dead macrophages and senescent adipocytes in adipose tissues of HFD-fed mice, suggesting possible senolytic effects. In this case, the polysaccharides may produce senolytic or senomorphic effects indirectly by modulating the gut microbiota and preventing lipopolysaccharide-induced metabolic endotoxemia, a possibility that remains to be examined.

Together, these results indicate that senolytics can alleviate the development of a wide range of chronic diseases.

4 | SENOMORPHICS: NEW FUNCTIONS FOR OLD COMPOUNDS

Instead of killing senescent cells, many compounds derived from plants, vegetables and dietary supplements prevent stressed cells from becoming senescent or, alternatively, these compounds reduce secondary senescence by blocking the SASP (Table 1). Candidates in this category of "senomorphics" include apigenin [**25**], 4,4'-dimethoxychalcone [**26**], glucosamine [**27**], kaempferol [**28**], nordihydroguaiaretic acid (NDGA) [**29**], and resveratrol [**30**]. For instance, resveratrol protects human endothelial cells and fibroblasts against stress-induced senescence.[59,60] While a high level of stress is detrimental to cells and organs, mild stress may be beneficial by activating cellular defense mechanisms, such as autophagy, mitochondrial biogenesis, DNA repair, and expression of antioxidant and detoxifying enzymes.[6-8,61,62] By inducing these cellular protective mechanisms, senomorphic compounds may lower the level of cellular stress, therefore preventing cells from entering senescence or apoptosis.[6-8,61-64]

Stress intensity may determine whether cells become senescent or apoptotic. A low amount of DNA damage may induce p21-mediated cell cycle arrest, allowing cells to repair DNA damage before re-entering the cell cycle.[65] Low doses of ultraviolet light, oxidants or DNA-damaging agents induce senescence in cultured cells, while high

doses induce apoptosis.[66] Yet, whether cells undergo senescence or apoptosis may also depend on cell type, as some cells are more sensitive than others. In some conditions, senescence may provide advantages over apoptosis since senescent cells can induce tissue repair while apoptotic cells cannot.[66]

Another strategy to target senescence is to suppress the SASP which drives inflammation and helps propagate secondary senescence in aging tissues (Figure 1).[16,17] The term "inflammaging" has been used to denote the common occurrence of chronic inflammation in aging individuals.[67] Many anti-inflammatory compounds are found in plants and fungi[45,68] and these may produce beneficial health effects at least in part by reducing the impact of SASP. Notably, mTOR activation drives the SASP program in senescent cells,[69] suggesting that mTOR inhibitors, such as rapamycin [**31**], NDGA and metformin may also provide health benefits by producing senomorphic effects. Many compounds found in plants and fungi inhibit mTOR activity, including caffeine [**32**], polyphenols, epicatechin [**33**], berberine [**34**], capsaicin [**35**], genistein [**36**] and curcumin.[7,8]

Recent studies suggest that cellular senescence may be reversible under some conditions. For instance, resveratrol analogs reduce the senescence markers $p16^{INK4/6}$ and SA-β-Gal by altering splicing factor expression in senescent fibroblasts.[70] For some of the resveratrol analogs examined, these effects were independent of sirtuin-1 (SIRT-1), SASP, and senolysis.

Yet, the use of senomorphics has one major drawback. In contrast to senolytics, which are effective when given in an intermittent manner, senomorphics may need to be taken regularly for an extended period to show benefits. As such, consuming a diet rich in phytochemicals from fruits and vegetables may provide health benefits at least in part by improving stress resistance and inducing senomorphic effects. While it remains to be seen whether senomorphics may produce health benefits in humans, people who regularly consume glucosamine or metformin live longer than non-users,[71-74] consistent with possible antiaging effects.

5 | CLINICAL TRIALS

In view of the positive results obtained in animal models, senolytic treatments have entered clinical trials. Preliminary results indicate that quercetin and dasatinib produce beneficial effects in humans with idiopathic pulmonary fibrosis.[75] A small open-label pilot study in which quercetin and dasatinib were administered 3 days per week for 3 weeks to 14 individuals with idiopathic pulmonary disease showed that senolytic treatment improved physical function, whereas frailty and the SASP index were unaltered. These results are encouraging given that treatments for conditions involving overt fibrosis are limited.

Another small open-label pilot study showed that quercetin and dasatinib given for 3 days reduced the number of senescent cells in the adipose tissues of nine subjects with diabetic kidney disease, while no effects were observed on skin senescence markers.[76] The senolytic cocktail also reduced crown-like structures in adipose tissues and circulating SASP factors and matrix metalloproteinases. Other clinical trials are currently under way to examine the effects of quercetin plus dasatinib as well as fisetin on markers of inflammation and frailty.

6 | REMAINING CHALLENGES AND FUTURE OPPORTUNITIES

Some senolytics and senomorphics derived from plants, including quercetin, fisetin, and glucosamine, are available as dietary supplements and are considered safe when used as recommended.[77,78] However, given that issues related to the composition and standardization of dietary supplements have been reported, we proposed earlier that manufacturers should confirm the safety and efficacy of dietary supplements.[79] These issues need to be addressed before senotherapeutics derived from plant sources and dietary supplements can be considered alongside pharmaceutical drugs.

Other plant-derived compounds that inhibit antiapoptotic pathways in previous studies may possess senolytic properties, including cyanidin, deguelin, delphinidin, epigallocatechin gallate, equol, and myricetin.[77] For instance, X-ray crystallography analysis indicated that the plant polyphenol myricetin binds to PI3K and inhibits its activity in a manner similar to quercetin.[80] Similarly, equol, a metabolite of genistein found in soybean, suppressed chemically-induced neoplastic transformation of mouse epidermal cells by inhibiting MEK1 kinase activity, which contributes to cell proliferation.[81] These compounds represent potential candidates for the identification of senolytics.

Chemical modification of plant-derived senolytic compounds may enhance their anti-senescence potency. For instance, a curcumin analog called EF24 [**37**] showed increased proapoptotic activity in senescent fibroblasts, compared with the mother compound.[82] Chemical modifications of piperlongumine led to the identification of analogs that possess increased potency and selectivity in killing senescent cells.[83] Another strategy is to deliver senolytics to specific tissues using carriers or nanomaterials. Silica nanoparticles coated with galacto-oligosaccharides (which are hydrolyzed by SA-β-Gal found at high levels in senescent cells) have been used to specifically deliver the organic dye rhodamine-B into senescent cells in vitro.[84] Cytotoxic drugs have also been targeted to senescent cells by conjugation with galactose or galacto-oligosaccharides.[85-87] In addition, local senolytic delivery to target organs, such as the articulations of osteoarthritic patients may also attenuate systemic side effects.

Senolytics are especially promising for improving the efficacy and reducing side effects of cancer treatment. Repeated cycles of chemotherapy or radiotherapy induce senescence in both normal tissues and tumors in cancer patients, producing side effects and limiting treatment efficacy.[16] In an experimental model, elimination of senescent cells in transgenic mice reduced chemotherapy side effects and cancer recurrence.[88] Senolytics may be combined with cancer treatment to induce clearance of senescent cells to prevent relapse, as senescent cells contribute to cancer development by inducing inflammation.[16] Furthermore, the senolytics and plant extracts described here offer a new strategy for reducing the detrimental effects of fibrosis induced by anticancer treatment. Other advantages of using senolytics include the lack of resistance to these compounds, as senescent cells do not divide, and the possibility of using senolytics intermittently, which may limit side effects. Arguably one of the most alluring features of senolytics is the possibility of treating many aging-related conditions at once, since aging is believed to be a common denominator in the development of many chronic diseases.

The heterogeneity of cellular pathways activated in senescent cells from different tissues remains an obstacle for the therapeutic use of senolytics, but new combinations of senolytics may overcome this limitation. Another challenge may be related to the beneficial role that senescent cells play in wound healing and cancer prevention. Intermittent treatment with senolytics has been shown to be effective, and this strategy may limit the impact of senescent cell depletion on wound healing. With regard to cancer, senolytic treatments may in fact be beneficial since senescent cells fuel tumorigenesis in nearby cells in aging organisms[17] and elimination of senescent cells can delay cancer development in transgenic mice.[27] Furthermore, senolytics may reduce or delay cancer by preventing senescence escape in precancerous lesions, a pivotal process that appears to occur for many types of cancer.[89]

7 | CONCLUSION

Many senolytics are promising candidates for improving health in humans as reduction of the senescent cell burden delays aging and retards the development of chronic diseases in animal models of atherosclerosis, type 2 diabetes, and Alzheimer's disease (Table 1). Clinical trials are currently underway to determine if the health benefits observed in animals can be reproduced in humans, and further studies are needed to determine the optimal senolytic regimens in terms of molecule combinations, doses and treatment schedule. Ongoing research in the field of senescence may also reveal important insights relevant for the clinical use of senolytics, especially regarding the changes occurring with time in senescence cells, the SASP, and their cellular fate.

Finally, the results of animal studies suggest that senescence in diseased organs is caused by chronic stress. While intrinsic stress, such as telomere erosion and aberrant DNA replication, contribute to disease progression, many lifestyle choices may also play a causal role, including smoking, alcohol intake, sunlight and toxin exposure, and overeating. In this case, it is unlikely that senolytic treatment may revert disease conditions in humans if chronic stress continues to occur daily. In addition, antiaging interventions, such as CR[90], exercise[91], and flavonoids found in the human diet[92], decrease senescent cell accumulation and the SASP in animal models and may also help reduce cellular stress, such as telomere erosion and DNA damage by inducing repair and reducing oxidative stress. These antiaging interventions could be combined with senolytics to reduce the burden of senescence in the aging human body. Interventions that maintain immune function during aging are also likely to be beneficial by reducing accumulation of senescent cells over time.

In conclusion, recent research in the field of aging has revolutionized the prevention and treatment of diseases by showing that the aging process and the development of chronic diseases can be delayed by simple interventions, such as intermittent fasting, exercise and a phytochemical-rich diet that is widely available, safe and easy to implement. Antiaging interventions should attract more attention given that the efficacy of current treatments for conditions, such as atherosclerosis, cancer and neurodegeneration, is limited. The use of senolytics offers yet another antiaging approach that could provide major health benefits.

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DISCLAIMER

Y-FK is president of Chang Gung Biotechnology. JDY is Chairman of the Board of Chang Gung Biotechnology. The authors have filed patents related to the preparation and use of medicinal mushrooms, probiotics, and phytochemicals.

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