REVIEW ARTICLE

Potential Role of Polyphenolic Flavonoids as Senotherapeutic Agents in Degenerative Diseases and Geroprotection

Kingsley C. Mbara[1] · Nikita Devnarain[1] · Peter M. O. Owira[1]

Abstract

Cellular senescence, a hallmark of ageing, contributes to tissue or organ dysfunction and the pathophysiology of diverse age-related diseases (ARD) by various mechanisms. Targeting it by selective elimination of senescent cells (SCs) or blocking senescence-associated secretory phenotypes (SASP) with natural or synthetic compounds has been suggested to improve lifespan. Dietary phytochemicals possess a broad spectrum of biochemical and pharmacological effects that are beneficial to human health. Flavonoids, which are widely consumed in fruits and vegetables worldwide, are emerging as potential therapeutic agents to mitigate senescence. Naringenin, hesperetin, hesperidin, quercetin, fisetin, kaempferol, rutin, apigenin, luteolin, nobiletin, tangeretin, genistein, wogonin, epigallocatechin gallate (EGCG), theaflavin-3-gallate (TF2A), and procyanidin C1 possess potent antisenescence effects. A single biochemical process may not explain their pleiotropic pharmacological impact. Flavonoids directly modulate underlying cellular senescence processes or interact with molecular targets that regulate ageing-related pathways. This review discusses the potential use of flavonoids to mitigate senescence and consequently delay the onset of ageing-related diseases. We also highlight the underlying mechanisms of action of flavonoids as potential senotherapeutics and reflect on future perspectives and possible strategies to optimize and increase the translatability from bench to bedside in senotherapy.

Key Points

Polyphenolic flavonoids are emerging as potential senotherapeutic agents.

Natural dietary flavonoids are multi-target compounds that can alleviate senescence in multiple organs by diverse mechanisms of action.

Polyphenolic flavonoids are protective against ageing-related degenerative diseases such as cancer, diabetes and cardiovascular diseases, with potential therapeutic applications.

Emerging preclinical evidence suggests that polyphenolic flavonoids could provide geroprotective effects.

✉ Peter M. O. Owira
owirap@ukzn.ac.za

1 Molecular and Clinical Pharmacology Research Laboratory, Department of Pharmacology, Discipline of Pharmaceutical Sciences, University of Kwazulu-Natal, P.O. Box X5401, Durban, South Africa

1 Introduction

The increased global life expectancy due to advances in healthcare has led to the increased incidence and burden of ageing and ageing-related diseases (ARDs). By 2050, the population of older people over 65 years is globally projected to be 1.6 billion, imposing a socioeconomic burden on a frail elderly population [1]. In ageing, the proliferating capacity of previously replication-competent cells decreases, leading to cellular senescence. This is a critical mechanism that contributes to ageing and ARDs, whereby cellular stress of proliferating or differentiated non-dividing cells results in a replicative arrest, apoptosis resistance, and pro-fibrotic, proinflammatory, and proinflammatory tissue-destructive senescence-associated secretory phenotype (SASP) [2]. Cellular senescence is a multifaceted process occurring in various somatic cells, and it is regulated by genetic, epigenetic, and environmental factors [3].

More specifically, senescent cells (SC) accumulate in many but not all tissues in aged mammalian organs [4]. This accumulation results from an imbalance between their generation and elimination. Senescent cells are metabolically active and capable of performing the functional roles of their original replication-competent cells. At senescence,

cells are stable and persistently growth-arrested, enlarged, and activate damage response signalling pathways [e.g., p38 mitogen-activated protein kinases (p38 MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)] as well as express senescence markers [e.g., senescence-associated β-galactosidase (SA-β-gal), p16^{INK4A}, and p21$^{WAF1/Cip1}$], thereby resulting in the development of DNA segments with chromatin alterations reinforcing senescence (DNA-SCARS) [5, 6]. Senescence has beneficial as well as harmful effects on physiological and pathological processes. Acute senescence contributes to preserving cellular/tissue homeostasis, tumour suppression, wound healing, embryonic development, tissue regeneration, and the promotion of insulin secretion by pancreatic β-cells during ageing [7]. Conversely, chronic senescence, which results in the accumulation of SCs and their SASP, exerts deleterious effects on physiological processes [6, 8]. This contributes substantially to the development and progression of ageing and ARDs, including atherosclerosis, type 2 diabetes mellitus (T2DM), cancers, neurodegenerative diseases, arthritis, renal dysfunction, blindness, frailty, and sarcopenia, among many others (Fig. 1). Therefore, both pro-senescence therapies and anti-senescence treatments can be beneficial depending on the context of senescence. As a corollary, targeting cellular senescence is crucial for healthy living, especially in ageing organisms.

The use of bioactive compounds in senotherapeutics has recently emerged as a promising approach to prolong the lifespan and reduce the severity of chronic diseases. Dietary phytochemicals can enhance the lifespan by modulating metabolic pathways and cellular processes in the same manner as other antiageing interventions such as caloric restriction, intermittent fasting, and exercise [9]. These beneficial effects of dietary phytochemicals from fruits and vegetables may be attributed to the activation of stress resistance pathways. Some natural senolytic compounds and pharmaceutical drugs exert anti-senescence effects by interacting with molecular targets to affect other ageing-related courses [10]. Naturally derived senolytics may be less potent but have the advantage of low toxicity when compared to synthetic senolytics and may be promising candidates for translation into clinical settings or for the development of more specific and potent senotherapeutics.

Polyphenolic flavonoids have beneficial effects on several age-related pathologies [11, 12]; hence, they can be harnessed as senotherapeutics. However, knowledge of their potential application in senotherapy is scanty. We, therefore, provide a brief background to senescence and senotherapeutics and now review the understanding of flavonoids as potential senotherapeutic agents and their mechanisms of action from experimental animal models to clinical trials.
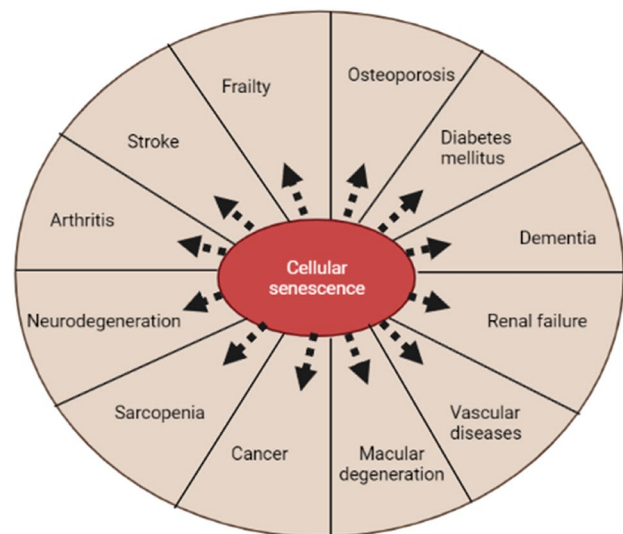

Fig. 1 The central role of cellular senescence in aging-related diseases. Figure created with BioRender.com

2 Senescent Cells

SCs abound in tissues at the late stages of life and sites of age-related pathologies, triggering disease processes through the complex cell and non-cell-autonomous effects [13]. Senescent cell phenotypes have standard core features in vitro and in vivo, even though the unique universal hallmarks of cell senescence are poorly understood. They are persistently growth-arrested and characterized by the absence of proliferation markers. SCs show altered morphology with generally enlarged and flattened cell shapes. Senescence is also characterized by high levels of lipofuscin, cell replication stimulatory proteins, SA-β-gal activity, and senescence-associated DNA markers with altered chromatin structure, such as senescence-associated DNA damage foci (SDF) and senescence-associated heterochromatin foci (SAHF) [14]. The available biomarkers developed thus far for cellular senescence are targeted towards SA-β-gal activity, telomere attrition, SAHF, cell cycle arrest, and accumulation of DNA damage with the expression of ataxia-telangiectasia mutated (ATM) kinase, p53, p16, and p21 [8]. To address the concern of not having a specific or universal biomarker, combining a collection of these biomarkers is generally accepted to define senescence in different cell types, both in cultured cells and tissues [15].

2.1 Senescence-Associated Secretory Phenotype (SASP)

The SASP is a distinctive feature that differentiates SCs from non-senescent cells and other cell cycle-arrested

cells, such as quiescent and terminally differentiated cells. The SASP consists of a distinct secretion of various cytokines, chemokines, growth factors, proteases, and lipids implicated in the pathogenesis of various chronic diseases associated with ageing and thus serve as the link between cellular senescence and inflammaging [7]. The components of SASP differ in composition depending on the cell type and senescence trigger, and are activated a few days after a persistent stimulus. The SASP exerts dual effects physiologically in a context-dependent manner. It has a vital role in promoting the repair of damaged tissues, immune surveillance/clearance of SC, and exerting tumour-suppressive effects; however, SASP promotes ageing, chronic inflammation and/or tumorigenesis by spreading senescence in both an autocrine and a paracrine manner [16].

Major inducers of SASP expression include DNA damage, mitogenic signals, oxidative stress, and epigenomic disruptions [17]. In contrast to senescence and cell-cycle arrest, SASP is independent of the ectopic expression of senescence factors such as p16^{Ink4a} and p21$^{Waf1/Cip1}$, suggesting that there are other signalling pathways in their induction [18, 19]. Although the precise mechanisms underlying SASP induction are yet to be elucidated, persistent genomic damage has been suggested to be responsible for SASP production, which is at variance with ectopic expression of p21 or p16 inhibitors [18].

3 Senotherapeutics

Pharmacological targeting of the fundamental mechanisms of ageing can reduce or delay the progression of ageing in both experimental animal models and humans. Senotherapeutics has emerged as a novel strategy in the pharmacotherapy of ageing-related diseases like cardiovascular diseases (CVD), diabetes, and cancer (Fig. 1) [4]. This new class of synthetic drugs and natural products neutralizes cellular senescence's adverse effects and ultimately prolongs lifespan. Senotherapy has gained prominence to the extent that some of these senotherapeutics are currently undergoing human clinical trials. Generally, senotherapeutic strategies include selective elimination of SC, referred to as senolysis, immune-mediated defence against SCs (immunosurveillance), and SASP neutralization. SCs are reduced by targeting networks of anti-apoptotic factors that promote their survival, suppressing the inflammatory SASP, and genetic modification using transgenic animals in activating apoptotic signals mediated by p16^{Ink4a} or p21^{Cip1} promoter elements [20, 21]. However, the classification of senotherapeutic agents remains a significant problem due to possible overlap among them and

an absence of knowledge of well-defined mechanism(s) of action. Nonetheless, the two prominent classes so far introduced for basic and clinical research are senolytics and senomorphics.

3.1 Senolytics

Senolytics are small molecules that act by selectively eliminating SCs either by apoptotic or nonapoptotic means. SCs typically withstand intrinsic and extrinsic proapoptotic signals, unlike normal cells using senescent cell anti-apoptotic pathways (SCAPs). This pro-survival feature enables them to stimulate diverse biological processes under stress conditions [22, 23]. Developing drugs that preferentially target these anti-apoptotic and pro-survival pathways, thereby protecting SCs from their SASP, leads to selective death of SCs and prevents their detrimental effects. Therefore, the development of senolytics focuses attention on such pro-survival (pro-senescence and anti-apoptotic) pathways, including B-cell lymphoma 2 (Bcl-2)/Bcl-xL, phosphatidylinositol 3-kinase (P13K)/protein kinase B (Akt), p53/p21/serpines, dependence receptors/tyrosine kinases, ephrins, hypoxia-inducible factor-1α (HIF-1α), and heat-shock protein 90 (Hsp90) [21, 23, 24], as well as the metabolic targets for the development of cellular senescence [25]. Many US Food and Drug Administration (FDA)-approved drugs, as well as phytochemicals and synthetic compounds, have been shown to possess potential senolytic activities [10, 26]. Table 1 summarises the identified senolytics, their sources, dosage forms, mechanisms of action, and their main effects in various pathological conditions.

Even though senolytics are meant to be specific for SC, there is always the concern of unwanted damage/side effects since the administration is not optimized [27]. Moreover, treatment with senolytics may also potentially target physiologically relevant SCs or other types of non-senescent cells, thereby raising the question of whether the treatment with senolytics could affect normal physiological conditions. In the light of this, novel therapeutic strategies, including the encapsulation of drugs using nanocapsules that preferentially introduce the toxin (senolytic) specifically to target SCs could be employed. Other therapeutic strategies for improving the efficacy and biosafety profile of senolytics include the use of proteolysis-targeting chimera (PROTAC) technology, local administration directly to insulated sites of interest, targeting of senescence-specific molecular targets, and the combinatorial approach [21, 28–30]. Senolytic activity can be assessed by considering the specificity for eliminating SC, resistance to apoptosis, autophagy regulation, and prolonging lifespan.

Table 1 List of compounds with senolytic activity

Senotherapeutic agents	Route/delivery system	Disease model	Target(s)	Source	Main findings	References
A1331852, A1155463	Conventional dosage form/oral	Aging and ARDs	Bcl-xL	Synthetic	↓ Senescent HUVECs and senescent human lung fibroblasts in vitro	[29]
ABT 737	Conventional dosage form/intraperitoneal	Aging and ARDs	Bcl-W and Bcl-xL inhibitor	Synthetic drug	↓ Senescent cells in lungs and epidermis of mice; ↑ hair-follicle stem cell proliferation in mice	[129]
Navitoclax (ABT263)	Conventional dosage form/oral and intraperitoneal	Aged tissue stem cells; chronic pulmonary fibrosis	Bcl-2, Bcl-xL and Bcl-W inhibitors	Synthetic drug	↑ Apoptosis and rejuvenated hematopoietic and muscle stem cells senescence in vivo; ↓ viability of senescent HUVECs, human lung fibroblasts and murine embryonic fibroblasts in vitro; ↓ senescent type II pneumocytes and alleviates ionizing radiation-induced pulmonary fibrosis in mice in vivo	[130–132]
GalNP(navitoclax) 6-mer β (1,4)-galacto-oligosaccharide; GalNP(navitoclax)	Mesoporous silica nanoparticles/intravenous	Cancer chemotherapy and pulmonary fibrosis; TNBC	SA-β-gal	GalNP(nav) 6-mer β (1,4)-galacto-oligosaccharide; GalNP(nav)	↑ Apoptosis and tumour regression in senescent xenograft tumours in vivo; ↓ tumour development and metastasis in vivo	[133, 134]
PZ15227 (PZ)	Proteolysis-targeting chimera (PROTAC) technology/intraperitoneal	Platelet toxicity	Bcl-xL	Bcl-2/XL binding moiety of ABT263 to a CRBN ligand	Eliminated SC and rejuvenates tissue stem and progenitor cells in aged mice	[30]
Dasatinib	Conventional dosage form/oral; molecularly imprinted nanoparticles (B2M nanoMIPs)/intravenous	Aging and ARDs	Ephrin receptors; B2M	Synthetic drug; B2M nanoMIPs loaded with dasatinib	↓ Viability and induced apoptosis of senescent human fat cell progenitors in vitro; ↑ Elimination of SC in vitro and in vivo	[21, 135]

Table 1 (continued)

Senotherapeutic agents	Route/delivery system	Disease model	Target(s)	Source	Main findings	References
Dasatinib + quercetin	Conventional dosage form/ oral	Multiple age-related co-morbidities	Bcl-XL, PI3K/Akt, p16, p21, p53, serpines, tyrosine kinase inhibitors, cleaved caspase-3, apoptosis	Combined (natural and synthetic)	↓ 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 wildtype 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	[2, 21, 40, 45, 52, 71, 73, 136–138]
Geldanamycin	Conventional dosage form/ oral	Premature aging	Hsp90	Synthetic	↓ Senescent murine embryonic fibroblasts in vitro; ↓ age-related symptoms in progeroid Ercc1$^{-/\Delta}$ mice	[136]
Azithromycin	Conventional dosage form/ intravenous and oral	Cystic fibrosis	Autophagy	Macrolide	↓ Viability of human senescent lung and skin fibroblasts in vitro	[139]
Tanespimycin	Conventional dosage form/ oral and intraperitoneal	Premature aging	Hsp90	Synthetic (geldanamycin derivative)	↓ Senescent murine embryonic fibroblasts in vitro	[136]
Roxithromycin	Conventional dosage form/ oral	Cystic fibrosis	Autophagy	Macrolide antibiotic	↓ Viability of human senescent lung and skin fibroblasts in vitro	[139]
P5091	Conventional dosage form/ intraperitoneal	Aging and ARDs	Usp7, p53, Bcl-xL and Bak	Synthetic	↑ SC apoptosis SC in vitro and in vivo	[140]
FOXO4-DRI peptide	Conventional dosage form/ intravenous	Aging and ARDs	p53, apoptosis	Synthetic	↑ Apoptosis of human senescent lung fibroblasts in vitro; ↑ fitness, ↑ fur density and ↑ kidney functions in aged Xpd$^{TTD/TTD}$ and wild-type mouse models	[141]
EF24	Conventional dosage form/ intraperitoneal	Ageing-related failure of tissue homeostasis	Bcl-2, apoptosis	Curcumin analog	↓ Viability of human senescent fibroblasts in vitro	[142]
Fenofibrate	Conventional dosage form/ oral	Cartilage ageing and osteo-arthritis	PPARα, autophagy, apoptosis	Synthetic	↓ Senescent chondrocytes in vitro	[143]

Table 1 (continued)

Senotherapeutic agents	Route/delivery system	Disease model	Target(s)	Source	Main findings	References
Cardiac glycosides (proscillaridin A, digoxin)	Conventional dosage form/intraperitoneal	Lung fibrosis	Na+/K+ ATPase, apoptosis	Natural (Plants)	↓ Human senescent lung adenocarcinoma A549 cells, primary fibroblasts, and osteoarthritic chondrocytes in vitro; ↓ improved the effects of chemotherapeutics against tumour xenografts in vivo; ↓ SC and fibrosis in a mouse model of lung fibrosis	[144]
Piperlongumine	Conventional dosage form/ oral and intraperitoneal	Senescent fibroblasts derived from lung tissue	Apoptosis, oxidation resistance 1 protein	Natural (plant)	↓ Senescent human WI-38 fibroblasts in vitro	[145, 146]
Panobinostat	Conventional dosage form/ oral	Chemotherapy-induced senescence	Histone 3 (H3) acetylation, Bcl-xL	Drug	↓ Senescent NSCLC and HNSCC cells in vitro	[147]

ARDs age-related diseases, *B2M* beta-2 (β2) macroglobulin, *Bcl* B-cell lymphoma, *EGCG* epigallocatechin gallate, *GalNP(nav)* 6-mer galacto-oligosaccharide encapsulated navitoclax, *HNSCC* head and neck squamous cell carcinomas, *HSP90* heat-shock protein 90, *hMSCs* human mesenchymal stem cells, *HUVECs* human umbilical vein epithelial cells, *IPF* idiopathic pulmonary fibrosis, *NSCLC* non-small-cell lung cancer, *PI3K* phosphoinositide 3-kinase, *PPARα* peroxisome proliferator-activated receptor alpha, *ROS* reactive oxygen species, *SA-β-Gal* senescence-associated β-galactosidase, *SASP* senescence-associated secretory phenotype, *SC* senescent cell, *TNBC* triple-negative breast cancer, *USP7* ubiquitin-specific peptidase 7

3.2 Senomorphics

Senomorphics are small molecules that suppress/reprogram SASP or proinflammatory secretome [10, 31]. Some molecules, however, may be categorized as senomorphics based on their ability to inhibit other biomarkers of cellular senescence without killing SC. Candidates in this class include natural and synthetic compounds and approved drugs to be repurposed for senotherapy (Table 2). The primary strategic approach of senomorphics is the targeting of regulatory pathways associated with SASP expressions, such as the p38 mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase/serine/threonine protein kinase (PI3K/Akt), mechanistic target of rapamycin (mTOR), and the Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathways, and transcription factors, such as NF-κB, CCAAT/enhancer binding protein-β (C/EBPβ) and STAT3 [32]. The other approach uses specific antibodies to target the activity and function of certain SASP factors such as interleukin (IL)-1α, IL-8, IL-6, and matrix-remodelling proteases such as A disintegrin and metalloprotease 17 (ADAM17) [27]. This strategy could provide a better way of alleviating safety concerns attributed to SASP. For instance, rapamycin, by targeting the expression of IL-6 and IL-1α, selectively inhibited the deleterious effects of senescence-associated inflammation, thereby facilitating the harmful impact of genotoxic exposures and normal ageing processes [33].

Although most senomorphics are specific in action, there is remarkable diversity in SASP occurring in the different SC populations. Understanding the biological significance of various SC types and the effects of their SASP components is needed to improve the target specificity of senomorphics in other pathological conditions [25]. However, a significant drawback is that blocking SASP leads to the inhibition of crucial pathways for the maintenance of tissue homeostasis. Another challenge is the clearing of SASP-silenced SCs by the immune system, considering that many SASP factors participate in the recruitment of immune cells. This will address the critical question as to whether the administration of senomorphics could compromise the normal function of tissues and organs [27]. However, these problems could be addressed by epigenetic control of SASP expression with chromatin modifiers. Senomorphics require improved biosafety profiles as they must be administered regularly over an extended period. Hence, consumption of dietary phytochemicals from fruits and vegetables may at least in part be a viable option to target SCs by improving stress resistance through various cellular protective mechanisms.

Table 2 List of compounds with senomorphic activity

Senotherapeutic agents	Route/delivery system	Disease model	Target(s)	Source	Main findings	References
Corticosterone, cortisol	Conventional dosage form/ oral and parenteral	Chronic low-grade inflammation	IL-1α/NF-κB	Hormone, drug	↓ SASP in human fibroblasts in vitro	[148]
Curcumin (analogs)	Conventional dosage form/ oral and parenteral	Inflammation and back pain	Nrf2, NF-κB, apoptosis	Turmeric, dietary supplement	↓ Senescent human IVD cells and ↓ SASP ex vivo	[149]
Glucosamine	Conventional dosage form/ oral and parenteral	Intervertebral disc degeneration	Autophagy	*Aspergillus niger*, dietary supplement	↓ Senescence of rat nucleus pulposus cells in vitro	[150]
Resveratrol	Conventional dosage form/ oral	Endothelial dysfunction, vascular inflammation	SIRT1, NF-κB (IκB-kinase)	Fruits, red wine, dietary supplement	↓ Senescence of human cells in vitro;	[151, 152]
Metformin	Conventional dosage form/ oral	Aging and ARDs	NF-κB, DICER1, Akt, p16, p21	Drug (derived from French lilac)	↓ SASP in human senescent lung fibroblasts in vitro; ↓ ceramide-induced senescence in myoblasts in vitro; ↓ human senescent lung fibroblasts in vitro	[153–155]
Ruxolitinib	Conventional dosage form/ oral	Aging and ARDs	JAK	Drug	↓ SASP in human primary preadipocytes and HUVECs in vitro; ↓ inflammation and ↑ physical function in aged mice	[156]
Rapamycin	Conventional dosage form/ oral and parenteral; Calcium carbonate (CaCO3) nanoparticles; PEGylated liposome	Premature aging, Stem cell senescence	mTOR, p16, p21, autophagy, ROS, NF-κB; CD9	*S. hygroscopicus*, macrolide antibiotic (drug); CD9-Lac/CaCO₃/Rapa; LR-CD9mAb	↓ 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 in vivo; ↓ senescent Ercc1⁻/⁻ murine embryonic fibroblasts in vitro; ↓ Senescence in human dermal fibroblasts	[33, 136, 157–159]; [160, 161]
Simvastatin	Conventional dosage form/ oral	Cancer	IL-6, protein prenylation, Rho GTPase	Drug (derived from *Aspergillus terreus*)	↓ SASP in human fibroblasts in vitro	[162]
KU-60019	Conventional dosage form/ oral and parenteral	Aging and ARDs	ATM kinase inhibitor	Synthetic	↑ Cell number, ↓ SA-β-gal activity, p16 expression and ROS levels in senescent fibroblasts in vitro	[163]

Table 2 (continued)

Senotherapeutic agents	Route/delivery system	Disease model	Target(s)	Source	Main findings	References
NBD peptide	Conventional dosage form/ intraperitoneal	Progeroid syndrome	IKK	Synthetic peptide	↓ SASP and delays age-related pathologies in mice	[164]

AMPK AMP-activated protein kinase, *ARDs* age-related diseases, *HUVECs* human umbilical vein epithelial cells, *IL-1α* interleukin-1α, *IVD* intervertebral disc, *mTOR* mechanistic target of rapamycin, *NBD* NEMO-binding domain peptide, *NDGA* nordihydroguaiaretic acid, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *Nrf2* nuclear factor (erythroid-derived 2)-related factor 2, *ROS* reactive oxygen species, *SASP* senescence-associated secretory phenotype, *SIRT-1* sirtuin-1, *TGF-β* transforming growth factor-β

3.3 Immune System-Mediated Clearance of Senescent Cells

SCs elicit immunogenic responses and can undergo immune surveillance in different immune system components. Immunosurveillance of SCs potentiates the immune system for efficient recognition and elimination of SC; hence, it is another viable strategy in senotherapy. Immune-mediated clearance of SCs can be achieved either by generally boosting the immune function to prevent immunosenescence or by promoting anti-senescent cell function [27]. Since the accumulation of SCs in aged tissues is associated with an intrinsic decline of immune function [34], therapeutic strategies to boost the immune system could lead to successful clearance of SCs from aged tissues. Anti-senescent cell functions can be improved by stimulating immune recognition molecules such as natural killer (NK)-cells, macrophages, and CD4+ T cells [23, 35]. Possible immune-senotherapeutic strategies include reducing the number of senescent immune cells with specific antibodies recognizing surface senescence markers [35], facilitating the expression of these receptors on the surface of SCs [36], and increasing the binding affinity of the cell-surface receptors on the membrane of SCs [37].

Other new interventions to improve the immune system in SC clearance have emerged as effective treatments for a wide variety of diseases. Considering the immunogenic nature of SC, the restoration of immune surveillance of chronic SCs or its manipulation to promote their immunogenicity are promising clinical development strategies.

4 Molecular Aspects of Senotherapeutics

The molecular mechanisms of senotherapeutics are closely associated with the various hallmarks of aging. These fundamental aging mechanisms include genomic instability, epigenetic changes, shortening of telomeres, mitochondrial dysfunction, loss of proteostasis or autophagy, dysregulated nutrient sensing, altered cellular communication, stem cell exhaustion, and reduced regeneration capacity [38]. Epigenetic modulations such as DNA methylation and histone post-translational modifications by senotherapeutics affect genomic integrity, gene expression, and pathophysiology of organisms. Senotherapeutics target and regulate mitochondrial homeostasis, cell-cycle proteins, transcription factors, autophagy, stem cell activity, intermediary metabolism, and several signalling pathways implicated in the induction of cellular senescence (Tables 1, 2).

5 The Imprint in Degenerative Diseases

Therapeutic targeting of cellular senescence has a significant impact on disease pathogenesis. It could be more effective at alleviating degenerative diseases and frailty progression than any currently available treatment options.

5.1 Diabetes and Dyslipidaemia

Like other ageing-related diseases, the development and accumulation of SCs are underlying features of diabetes and obesity. SCs are implicated in tissue dysfunction and comorbidities associated with diabetes and obesity. They may negatively contribute to type 1 and 2 diabetes pathogenesis by directly impacting pancreatic β-cell function, SASP-mediated tissue damage, and facilitating adipose tissue dysfunction [39].

5.2 Cardiovascular Diseases

SCs are critical drivers of atherosclerotic plaque formation in the endothelium and vascular smooth muscle. Roos et al. [40] reported that depletion of SCs led to improved vasomotor dysfunction and decreased calcified plaque formation in ageing animals, indicating the importance of SCs in endothelial dysfunction, a pathologic event in developing atherosclerosis.

5.3 Cancer

Uncontrolled proliferation and metastasis are characteristic features of cancer. Like other ARDs, ageing and senescence play significant roles in cancer development [41]. SCs have been shown to promote tumorigenesis by both cell and non-cell-autonomous mechanisms, contrary to the previously established tumour-suppressive roles of senescence-associated cell cycle arrest. The pharmacological approach of combining senescence-inducing cancer therapies with senolytics would be a viable option for reducing the risk of senescent cancer cells stemness, cancer growth, and the side effects of cancer therapy [42].

5.4 Renal Diseases

Ageing and SC abundance have been implicated in renal complications such as glomerulosclerosis and nephropathies [43]. Pharmacological clearance of SCs accumulated in various kidney compartments will ameliorate renal ageing and conditions.

5.5 Liver Diseases

The onset of chronic liver diseases, such as non-alcoholic fatty liver disease (NAFLD), hepatic inflammation, steatosis, cirrhosis, jaundice, hepatic encephalopathy, portal hypertension, and hepatocellular carcinoma (HCC), are common geriatric diseases closely linked to cellular senescence [44]. Elimination of SCs using a senolytic alleviated hepatic steatosis and portal inflammation, necrosis, and fibrosis in the liver of ageing mice [45].

5.6 Osteoarthritis

Osteoarthritis (OA) is a chronic degenerative disorder involving movable joints and is the leading cause of chronic pain and disability among older people. Ageing and tissue regeneration during traumatic injuries promote the accumulation of SCs in cartilage tissues [28, 46]. Pharmacological targeting of the antiapoptotic proteins and senomorphics attenuates SASP secretion and the development of post-traumatic OA in rats [47].

5.7 Lung Diseases

Idiopathic pulmonary fibrosis (IPF), characterized by radiographically evident interstitial remodelling, is a fatal, chronic, progressive, and fibrotic age-related lung disease driven by abnormally activated alveolar epithelial cells [48]. Cellular senescence through SASP has promoted functional lung deterioration in IPF. Hence, pharmacological targeting of cell senescence with senotherapeutics would mitigate fibrotic lung disease.

5.8 Neurological Disorders

Ageing predisposes to neurological disorders, especially Alzheimer's and Parkinson's disease. A close correlation between cell senescence and ageing and age-related neurodegeneration has been observed. Cellular senescence plays a significant role in several neurodegenerative disorders. Pathological changes occurring in the brain in Alzheimer's and Parkinson's diseases share similar characteristics with cellular senescence phenotypes [49]. Pharmacological intervention with senotherapeutics improved these neurological disorders.

6 Polyphenolic Flavonoids

Flavonoids are natural polyphenolic substances commonly found in fruits and vegetables and classified into different subtypes (Fig. 2). They contain a 2-phenyl-benzo-pyrane

backbone consisting of two benzene rings (A and B) bound to a 3-carbon unit heterocyclic pyran ring (C6–C3–C6), which is vital for their classification. Polyphenolic flavonoids are stored predominantly as glycosides in the cell vacuole of plants since glycosylation increases their solubility in water and decreases their reactivity. Hence, most flavonoids exist naturally as products of aglycones and sugars, mainly D-glucose and L-rhamnose, linked to the hydroxyl group at the C-3 or C-7 position.

Flavonoids possess a wide range of pharmacological properties and are promising candidates in anti-ageing research. Their effects are pleiotropic and influence cellular lifespan, SA-β-gal activity, and other markers of senescence directly or indirectly (Table 3). Such effects include maintaining SASP, inducing apoptosis in SCs, and activating different protective cellular mechanisms. Although the precise mechanisms of action have not been elucidated, their antioxidant and anti-inflammatory activities have been suggested to play a vital role since they are the main factors implicated in ageing and various ageing-related diseases [12, 50, 51]. Ample evidence from experimental animal studies has shown the anti-senescence effects of

flavonoids to be senomorphic, with only a few exerting senolytic effects [4, 5, 52–54].

6.1 Flavanones

6.1.1 Naringenin

Naringenin, the aglycone product of the enzymatic hydrolysis of the main bitter flavonoid naringin, has long been considered to possess various biological activities such as antioxidant, anti-inflammatory, antiproliferative, anti-dyslipidaemic, and antidiabetic effects [55]. Naringenin has been shown to improve neurogenesis in the brain of ageing mice through downregulation of tumour necrosis factor α (TNF-α) signalling pathway gene expression [56], suggesting its role in facilitating neurological impairment and cognitive ageing. Naringenin modulates oxidative stress and mitochondrial metabolic activity, leading to myoblast cells' abrogation of H_2O_2-induced senescence [57]. These findings suggest its importance in treating cardiometabolic disorders caused by a redox imbalance in the cell. Naringenin promotes the synthesis of the ECM of cartilage and, in turn, improves ageing

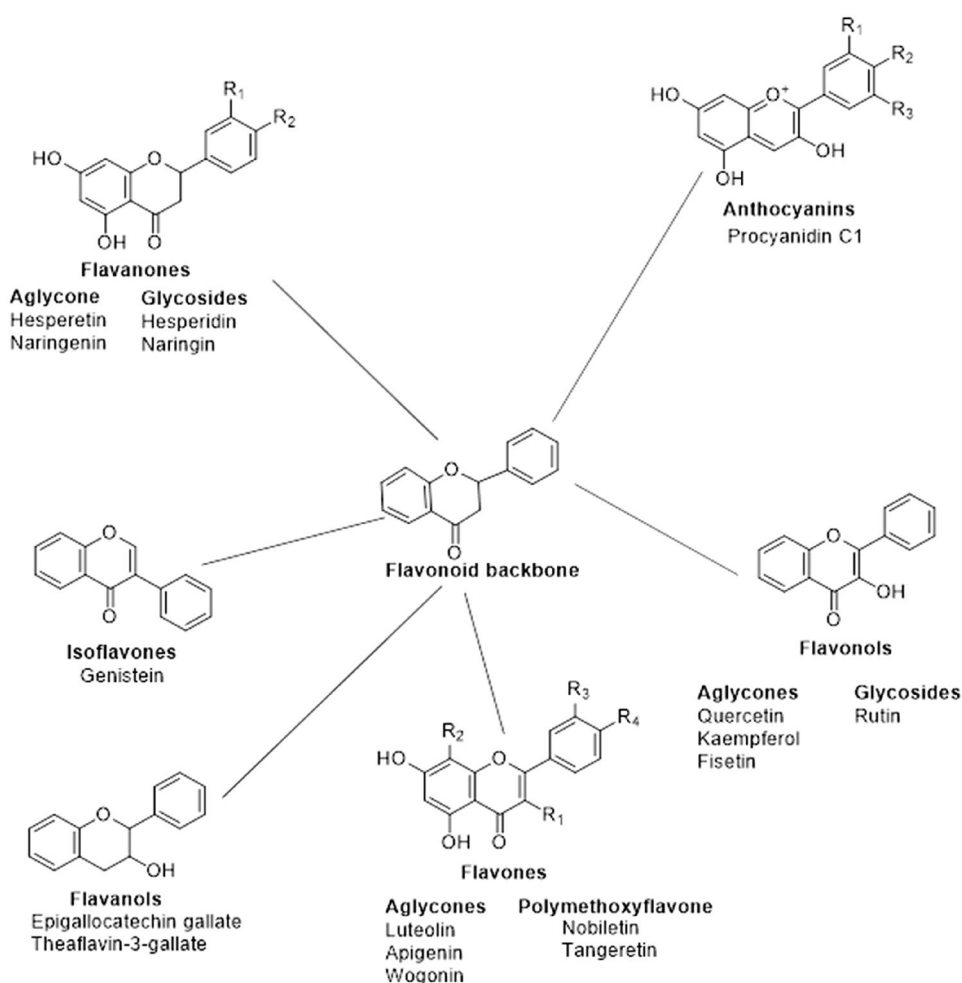**Fig. 2** Chemical structures of representative flavonoids classes with senotherapeutic effects

Table 3 Flavonoids and their underlying senotherapeutic effects

Flavonoid	Mechanisms	Biological activity	References
Apigenin	↓ NFκB, ↓ p38 MAPK	↓ SASP in human foreskin fibroblast; ↓ SASP in kidneys of aged rats	[5, 81]
Genistein	↑ Autophagy	↓ Senescent vascular cells in vitro	[101, 165]
Hesperidin	↓ ROS, ↓ NFκB, ↑ p53, ↑ Nrf2, ↑ Apoptosis	↓ SASP and cell senescence in H_2O_2-injured chondrocytes; improve aging-induced bone loss in male gonad-intact senescent rats	[62, 63, 166, 167]
Hesperitin	↓ JAK	↓ Inflammation in SW982 human synovial cells	[66]
Kaempferol	↓ NFκB, ↓ ROS, ↑ SIRT1	↓ SASP in human foreskin fibroblast; ↑ thermo-tolerance against lethal thermal stress; ↓ SASP in fibroblast	[5, 77, 168]
Luteolin	↓ ROS, ↓ NFκB	↓ SASP from keratinocytes; ↓ photoaging in keratinocytes and fibroblast; showed weak senolytic activity in fibroblast	[76, 83, 169]
Naringenin	↓ TNF-α, ↓ NFκB, ↑ SIRT1, ↑ Nrf2, ↓ NADPH oxidase	↓ Inflammation in senescent neural cells; ↓ SASP in hairless mice; ↓ senescent cells in HDF	[56, 133, 170, 171]
Nobiletin	↓ Bcl-2, ↑ Bax, ↑ Apoptosis, ↓ PI3K/Akt, ↓ NFκB	↓ SASP in hepatic senescent cells; ↓ SASP in senescent chondrocytes	[93–95]
Quercetin	↓ ROS, ↓ Bcl-xL, ↓ PI3K/Akt, ↓ p16, ↓ p21, ↓ NFκB, ↑ Nrf2, ↑ apoptosis	↓ Senescent human cells in vitro; ↓ SASP in fibroblast; ↓ SASP in nucleus pulposus cells in vitro; rejuvenates senescent human fibroblast	[21, 45, 67, 72, 172–174]
Rutin	↓ ROS	↓ Senescent VSMCs in mice	[78]
Tangeretin	↑ Apoptosis, ↓ NFκB	Proapoptotic effect on senescent cells, ↓ proinflammatory cytokines (SASP) in vitro	[96–98, 175]
Fisetin	↓ p16, ↓ p21, ↑ cleaved caspase-3/7, ↑ apoptosis, ↓ PI3K/Akt and ↓ ROS	↓ Senescent human cells in vitro; ↓ SC and ↓ SASP in progeroid and aged mice in vivo; ↓ age-related diseases and ↑ lifespan of wild-type, aged mice	[29, 76]
Wogonin	↓ NFκB, ↓ p38 MAPK, p53 and p21	↓ SASP in human foreskin fibroblast	[5]
EGCG	↑ Nrf2, ↑ SIRT3, ↓ PI3K/Akt/mTOR, ↓ AMPK, ↓ ROS and ↑ apoptosis	↓ SASP in senescent preadipocyte cells in vitro; ↓ SC and ↓ SASP in senescent preadipocyte cells in vitro	[102, 103]
TF2A	↓ p16, ↓ Hsp90	↓ Senescent hypothalamic neural stem cells in mice; ↓ SC in vivo	[104, 105]
Procyanidin C1	↓ ROS, ↑ Apoptosis	↓ SASP at low concentration and ↓ SC at high concentration in senescent stromal cells in vitro; ↓ SC in irradiated, senescent cell-implanted or naturally aged mice	[61]

in both lipopolysaccharide- and reactive oxygen species (ROS)-induced skin senescence through SIRT1-mediated inhibition of NF-κB, NADPH oxidase, and matrix metalloproteinases (MMPs) expression in human dermal fibroblast, suggesting regenerative and anti-ageing effects on the dermal cell structure [58]. However, Lim et al. [5] reported that naringenin did not suppress SASP production in bleomycin-induced senescence. This could be due to variation in the senescence-inducing mechanisms, which affects the composition of SASP factors. Moreover, our research group and others have reported that naringenin has known anti-inflammatory effects and shares similar pharmacological effects with the biguanide derivative metformin, which has

established senomorphic effects [55, 59–61]. However, more evidence from preclinical and clinical studies is required to support these findings.

6.1.2 Hesperidin and Hesperetin

Hesperidin and its aglycone, hesperetin, are major flavanones found in fruits and vegetables and have known antioxidant and anti-inflammatory effects that inhibit the production of proinflammatory cytokines, leading to the blocking of SASP [62–64]. They exert their senomorphic effects by modulating signalling pathways involving the Nrf2, NF-κB, and FOXO, and increasing antioxidant enzyme activity [63, 65].

Hesperidin has been shown to stabilize SASP and exerts anabolic effects in human senescent chondrocytes by increasing cellular antioxidant capacity and decreasing proinflammatory cytokines that constitute SASP, suggesting a beneficial role in the progression of OA [63]. Similarly, hesperidin has been shown to protect against bone loss by inhibiting bone resorption, NF-kB activity, and improving bone mineral density in male senescent rats [62, 65], suggesting a role in reducing the risk of fractures. Hesperetin plays a pivotal role in lowering immune inflammation of the joints in rheumatoid arthritis by inhibiting cytokine production and c-Jun N-terminal kinase (JNK) activity in synovial fibroblasts [66]. These potential anti-SASP mechanisms of hesperidin and/or hesperetin need to be considered in future clinical studies.

6.2 Flavonols

6.2.1 Quercetin

Quercetin is recognized for its many pharmacological activities, including anticancer, antidiabetic, anti-inflammatory, anti-atherosclerotic, antithrombotic, antihypertensive effects, and benefits for human endurance exercise capacity. The antioxidant activity of quercetin is a prominent characteristic that enables it to quench the formation of resonance-stabilized phenoxyl radicals from free radicals. Besides its antioxidant activity, Chondrogianni et al. demonstrated the anti-ageing and rejuvenating effect of quercetin on senescent human fibroblasts [67], as well as prolonging organismal life expectancy in *Saccharomyces cerevisiae* [68] and *Caenorhabditis elegans* [69]. Quercetin has been shown to alleviate cellular phenotypes of Hutchinson–Gilford progeria syndrome by reducing ROS, enhancing cell proliferation, and restoring heterochromatin architecture in premature ageing human mesenchymal stem cells [70], suggesting a role in maintaining skin turgidity. It is worth mentioning that quercetin is both senolytic and senomorphic as it modulates p53/p21/serpines or PI3K/Akt/mTOR and NF-κB signalling pathways [21, 71, 72], which results in reduced ROS production. However, quercetin had to be combined with dasatinib for more effective and broad-spectrum senolytic effects [21].

The senolytic cocktail of dasatinib and quercetin (D + Q), discovered using a hypothesis-driven bioinformatics approach, had direct senolytic effects on senescent adipocytes and human umbilical vein endothelial cells by disabling the pro-survival and anti-apoptotic pathways of the SCs [21]. Clinically, the senolytic combination of D+Q is safe and effective in alleviating physical dysfunction in patients with idiopathic pulmonary fibrosis [2], reducing inflammation (in the form of circulating SASP factors) and SC abundance in the skin and adipose tissue of patients with diabetes-related kidney diseases [73]. However, the use of the senolytic regimen has not been adopted in clinical

practice because of (1) inadequate knowledge of the systemic effects, (2) the precise context in which quercetin could be administered, and (3) interference with other biological pathways while inhibiting the specific SCAPs. Moreover, quercetin alone or in combination with dasatinib has been subjected to other clinical trials for coronary artery disease (NCT04907253), Alzheimer's disease (AD) (NCT04063124, NCT04785300, NCT04685590, NCT05422885), hematopoietic stem cell transplant survivors (NCT02652052), elderly frail patients (NCT04313634), and patient's epigenetic aging rate (NCT04946383).

6.2.2 Fisetin

Fisetin is another dietary flavonol present in fruits and vegetables such as strawberries, onions, cucumbers, and grapes, with a known safety profile [74]. Fisetin, just like its analog quercetin, acts on numerous biological processes that may also contribute to its senolytic effects. For instance, because of its hydrophobic nature, fisetin penetrates and accumulates in the cell membrane to exert antioxidant and inflammatory effects [29], and also induces apoptotic effects in SCs [75] by suppressing Bcl-2 family members and other SCAP network components. Fisetin suppressed multiple SC viability and increased lifespan by inhibiting pro-senescence effectors such as p16[Ink4a] and p21[Cip1] in wild-type mice [76]. Fisetin showed more enhanced senotherapeutic activity than quercetin in animal and human tissues [29], and is currently undergoing several clinical trials for multiple ARD, including osteoarthritis (NCT04815902, NCT04210986, NCT04770064), coronavirus infection (NCT04771611, NCT04476953, NCT04537299), frail elderly syndrome (NCT03675724, NCT04733534, NCT03430037), chronic kidney diseases (NCT03325322), and femoroacetabular impingement (NCT05025956). Therefore, the clinical merits of fisetin in terms of feasibility, safety, tolerability, and efficacy could soon be established and employed in geriatric medicine.

6.2.3 Kaempferol

Kaempferol is considered to have strong senomorphic effects by modulating various transcription factors and stress response signalling pathways such as oxidative stress and inflammatory responses. Kaempferol has been shown to reduce SASP levels by blocking IκBζ expression in aged rats, suggesting its role in alleviating chronic low-grade inflammation associated with many ageing-related diseases [5]. Kaempferol relieves oxidative stress and acts as an antigerontic agent by increasing DAF-16/FOXO activity in living transgenic worms *C. elegans,* resulting in attenuation of lipofuscin accumulation [77]. Consequently, although there is little direct evidence of kaempferol in senotherapy, such

anti-senescence effects could be expected in further studies owing to its prominent anti-inflammatory activity.

6.2.4 Rutin

Rutin, a glycoside of quercetin, attenuates atherosclerotic plaques in mice by improving metabolic disturbances and preserving oxidative stress, suggesting a role in alleviating fatal complications of diabetes associated with aberrant vascular smooth muscle cell (VSMC) proliferation, and premature senescence [78]. The anti-senescence effect of rutin appears to be because of its antioxidant, anti-inflammatory activity, and the transformation of rutin to its aglycone, quercetin, which has superior pharmacological effects [79, 80].

6.3 Flavones

6.3.1 Apigenin

Apigenin, belonging to the flavone subclass of flavonoids, is present in various fruits and vegetables. Apigenin has long-established antioxidant, anti-inflammatory, anti-mutagenic, and anti-proliferative effects [5, 81]. It appears to inhibit NF-κB activity by blocking translocation and phosphorylation of IκBζ, leading to the prevention of low-grade inflammation and the associated degenerative diseases [5]. The double bond and hydroxyl group substitution at the A and B ring of the flavonoid's backbone, which chelate metal ions and/or scavenges free radicals, could be responsible for the senomorphics effects of apigenin. Apigenin is now known to induce apoptosis in a p53-independent pathway by enhancing oxidative stress [82]. The p53-independent apoptotic effects of apigenin would support its use as a senolytic and in chemoprevention in neoplasm. Therefore, the potential senolytic effects of apigenin need to be considered in further studies.

6.3.2 Luteolin

Luteolin, which acts as the first-line defence system in plants against adverse photobiological effects such as protection against UV radiation, has shown promising senotherapeutic effects [83]. Luteolin regulates the expression of inflammatory cytokines, leading to the blockade of NF-κB's nuclear translocation and an abrogation of senescent murine embryonic fibroblast cells [76, 84], suggesting a beneficial role to patients with inflammatory disorders of the lungs. The anti-senescence effects of luteolin may be attributed in part to its anti-inflammatory, antioxidative capacities and proapoptotic effects. Luteolin suppresses proinflammatory SASP factors and regulates various signalling pathways implicated

in cellular senescence, such as NF-κB, JAK/STAT, and toll-like receptors (TLRs) [83]. Considering the structural activity relationship, the C2–C3 double bond at the A and B rings of luteolin could enhance the senotherapeutic effects of luteolin, just like apigenin. A clinical trial investigating the therapeutic effect of luteolin combined with palmitoylethanolamide in patients with frontotemporal dementia is underway (NCT04489017).

6.3.3 Wogonin

Wogonin, the active monoflavonoid constituent of the Chinese herbal tea from *Scutellari baicalensis* Georgi, has known antioxidant, anti-inflammatory, antiproliferative, and antimicrobial activities [85]. Wogonin is suggested to have senolytic effects by inducing cellular apoptosis through upregulation of p53 and p21 proteins [86]. In senescent human foreskin fibroblasts, wogonin alleviated SASP by down-regulating the NF-κB pathway [5], suggesting its potential therapeutic role in skin ageing. Wogonin, just like other flavonoids, is rapidly metabolized and excreted in the liver and intestine, which affects its efficacy and absorption rates. In order to improve the bioavailability and efficacy of the poorly absorbed wogonin, analogs such as GL-V9 with a broad spectrum of action have been formulated through structural modifications. In a recent report, GL-V9 showed potential senolytic effects against senescent breast cancer cells mediated through ROS-dependent apoptotic mechanism [87]. Thus, further research on the anti-senescence effects of wogonin and GL-V9 in other senescence-associated diseases is required.

6.4 Polymethoxyflavones

6.4.1 Nobiletin

Nobiletin (5, 6, 7, 8, 3′, 4′-hexamethoxyfavone) is a polyethoxylated flavonoid found in fruits and vegetables and has a broad range of pharmacological activities such as pro-apoptotic, anti-inflammatory, anti-tumour, antioxidant, and anti-diabetes [88]. Nobiletin has known promising anti-ageing and lifespan-extending effects [89, 90]. This could be because of the ability of nobiletin to interact with other molecular targets to produce extra bioactivities other than senescence. For instance, nobiletin interacts with cyclooxygenases, inducible NO synthase proteins, prostaglandin E2, MAPK, AMPK, and MMPs, exerting proapoptotic, anti-inflammatory, and anti-cancer effects [91–93]. By enhancing autophagy and mitochondrial recovery through the SIRT-1/FOXO3a and PGC-1α pathways, respectively, nobiletin reverses hepatic tissue damage in mice [94], suggesting a role in protecting the liver from ischaemia–reperfusion injury. In human chondrocytes, nobiletin treatment improved

the synthesis of ECM proteins. It abrogated articular carti-lage degradation by reducing the expression of inflamma-tory cytokines and preventing the activation of PI3K/Akt and NF-κB [95]. This suggests that nobiletin could confer structural support and enhance physical function in patients with OA. Collectively, these findings suggest potential seno-therapeutic effects of nobiletin but need to be corroborated in further preclinical and clinical studies.

6.4.2 Tangeretin

The senotherapeutic effects of the polymethoxyflavone tan-geretin appear to depend on its anti-inflammatory and apop-totic effects [96, 97]. Tangeretin has known apoptotic effects of inhibiting anti-apoptotic protein Bcl-2 and Bcl-xl and mod-ulating the PI3K/Akt signalling pathway [96], which can be argued to be senolytic by making SCs susceptible to their pro-apoptotic microenvironment. Tangeretin prevented ischae-mic and reperfusion-induced neuronal damage by inhibiting NF-κB activity, reducing oxidative stress, and decreasing pro-inflammatory cytokines in the brain of rats [97], suggesting its beneficial role in patients with ischaemic stroke. Tangeretin alleviates activated microglia-induced neuroinflammation by reducing proinflammatory cytokines and suppressing NF-κB and MAPK signalling [98], suggesting its valuable role in patients with neurodegenerative diseases.

6.5 Isoflavones

6.5.1 Genistein

The isoflavone genistein, which acts as a selective estro-gen receptor modulator, is found in citrus fruits [99, 100]. Genistein attenuates senescence in human vascular smooth muscle cells (VSMCs) by inhibiting mTOR activity and acti-vating autophagy [101], supporting its therapeutic poten-tial in age-related vascular diseases such as atherosclerosis. The genistein-dependent autophagy induction in vascular cells was mediated by liver kinase B1 (LKB1)–AMPK sig-nalling pathways. Genistein could function as a potential rapamycin analog (a known senomorphic agent) with little or no side effects by inhibiting mTOR. A clinical trial on the therapeutic effect of genistein in AD patients is ongoing (NCT01982578). Hence, further preclinical and clinical evi-dence on the senotherapeutic effects of genistein is necessary to promote its translation to geriatric medicine.

6.6 Flavanols

6.6.1 Epigallocatechin Gallate

The phytochemical epigallocatechin gallate (EGCG) is the major catechin found in green tea, with many potential benefits on health outcomes, including cell senescence, ageing, and ARD. Preclinical evidence suggests that EGCG exhibits promising senolytic and senomorphic effects through multi-faceted mechanisms, including targeting apoptotic pathways, cell cycle regulation, nutrient sensing pathways, SASP, and oxi-inflammatory stress pathways [102, 103]. EGCG attenuated DNA damage, cell cycle arrest, SASP formation, and induced apoptosis by inhibiting Bcl-2 and mTOR pathway in senescent preadipocytes [102], sug-gesting a central role in ageing and senescence-associated diseases. By activating the regulatory transcription factors Nrf2 and SIRT3, EGCG enhanced the antioxidant defences and alleviated SASP production in senescent preadipocytes [103], suggesting a beneficial role in both aging and obesity. The senotherapeutic mechanisms of action of EGCG are far from being fully understood and require further preclinical and clinical data validation.

6.7 Other Polyphenolic Flavonoids

Other polyphenolic flavonoids, including the oxidation and polymerization products of flavonoids such as theaflavin 3-gallate (TF2A) and procyanidin C1, have been shown to possess senotherapeutic effects in animals [104–106]. Theaflavins, the core functional polyphenols responsible for the red colour of black tea, have various biological activities, such as free radical scavenging and antioxidant, antiapoptotic, and anti-inflammatory activities [107]. TF2A exerted anti-senescence effect by mimicking and modulating the gene expression of long non-coding RNAs (LncRNAs). TF2A alleviated senescence of hypothalamic neural stem cells [104], bone marrow mesenchymal stem cells [105], and respectively improved aging-related phenotypes and bone regeneration in mice by stabilizing or delaying the degra-dation of Y-box protein 1 (YB-1), a transcriptional repres-sor of the senescence marker gene p16^{INK4A}. Thus, TF2A could be a promising candidate for stem cell regenerative application in patients with osteoporosis. Moreover, TF2A has been shown as a natural antagonist for Hsp90 [107], a known pharmacological target for senolytics, suggesting its prospects as a lead compound in the design of new seno-therapeutics, after rigorous validation approaches.

The polyphenolic flavonoid procyanidin C1 (PCC1) iso-lated from grape seed extract has been shown as a novel phytochemical senotherapeutic with superior specificity and efficiency for a wider range of SC types and senescence inducers than many reported senolytics [106]. PCC1 was reported to be senomorphic at low concentrations and seno-lytic upon treatment at higher concentrations, which could be suggested to be responsible for the elimination of SC, increased lifespan, and improved physiological functions in preclinical studies [106]. The senotherapeutic mechanism of PCC1 could, at least to some extent, be suggested to be

by downregulating proinflammatory gene expression and promoting ROS and mitochondrial-dependent apoptosis induction.

7 Clinical Considerations

Due to their cell-type specificity and unknown safety profile, currently available senotherapeutics should not be used to treat the various multimorbidities associated with cellular senescence. Natural dietary flavonoids are multi-target compounds that can alleviate senescence in multiple organs by diverse mechanisms of action. Unlike toxic synthetic agents, polyphenolic flavonoids have an improved tolerance profile and are cheaper in most cases.

Several epidemiological studies have reported that increased consumption of flavonoids is inversely correlated with the risk of CVD and T2DM [108, 109]. The pharmacological effects of flavonoids on atherosclerosis and CVD may be attributed to their ability to lower oxidative stress, hyperlipidaemia, and inflammation, and alleviate endothelial function, arterial blood pressure, and lipid metabolism [110]. For these experimental observations to be translated into clinical practice, optimization of bioavailability, and determination of dosage forms, delivery systems have to be determined. Epidemiologic data from 34,489 postmenopausal women demonstrated that consuming foods rich in flavonoids was inversely associated with all-cause mortality due to coronary heart disease and CVD [111]. Consumption of naringenin in the form of naringin has been associated with a reduced risk of CVD by improving the lipid profile in hypercholesterolemic patients [112] and exerting significant antihypertensive effects in patients with stage I hypertension [113].

Flavonoids regulate molecular events involved in the process of atherogenesis. Daily oral intake of hesperidin improved vascular reactivity and endothelial function, reduced inflammation, and favourably altered lipid profiles in patients with metabolic syndrome [64]. Moreover, hesperidin abrogated the development of atherosclerotic plaque formation by reducing adhesion molecules of endothelial cells [114]. These findings may reduce the risk of developing stroke in patients with metabolic syndrome.

Preclinical evidence suggests the beneficial effects of flavonoids on glucose intolerance, insulin secretion and sensitivity, insulin resistance [115], hepatic glucose output and intestinal glucose absorption [116], peripheral glucose uptake [117], inflammation [115], and the activity of enzymes and transporters involved in glucose and lipid metabolism [115, 118], suggesting their potential as an antidiabetic treatment regimen, especially among older people. They can cross the blood–brain barrier to exert antioxidative, anti-inflammatory, and neuroprotective effects on neural

cells and hence are promising candidates for alleviating age-related neurodegenerative disorders. Apigenin improves AD-associated learning and memory impairment by reducing amyloid-β peptides (Aβ) accumulation, inhibiting oxidative stress, and restoring cerebral BDNF levels [119], suggesting a role in preserving brain function in ageing. Naringenin has been shown to inhibit acetylcholinesterase activity and reduce neurotoxic effects of Aβ deposition in animals [120], suggesting its potential role in treating patients with dementia. Treatment with hesperidin or hesperetin ameliorated the development of AD and improved glucose metabolism by downregulating Aβ-induced autophagy in insulin-stimulated neuronal cells [121], suggesting a beneficial role in elderly patients with diabetes and AD comorbidities.

Several preclinical studies have demonstrated the chemopreventive effects of flavonoids, such as flavanones and polymethoxyflavones, on both cancer and non-cancer diseases [122]. Research on the anti-cancer activity of flavonoids has mainly focused on elucidating anti-proliferative effects, enzyme inhibition, and cytotoxicity in vitro and in vivo. They have consequently been shown to exert anticancer activity by alleviating chemotherapy resistance and synergizing with chemotherapeutic drugs to induce apoptosis of sensitive cancer cells [123, 124]. Their ability to halt cell cycle modulation, antiangiogenic effects, apoptosis induction, inflammation, and oxidative stress may be responsible for their beneficial roles in various types of cancers such as gastric cancer, colon cancer, breast cancer, lung cancer, and hepatomas. Furthermore, the structural similarities between flavonoids and 17β-estradiol could be associated with anti-estrogenic effects that could mitigate breast cancer.

A population-based, case–control study of lung cancer showed that dietary intake of quercetin and naringin conferred protection against lung cancer in Hawaiian patients [125]. Flavonoids are effective inhibitors of cancer invasion and metastasis by interfering with metastatic cascades, including cell–cell attachment, tissue-barrier degradation, migration, invasion, cell-matrix adhesion, and angiogenesis. In brain tumour cells isolated as surgical samples from patients, nobiletin and tangeretin suppressed brain tumour invasion by reducing gelatinase secretion, adhesion, and migration [126], indicating a role in patients with malignant gliomas.

Apart from their beneficial metabolic effects, flavonoids could be considered suitable adjuvants in treating human immunodeficiency virus type (HIV) infection-induced immune senescence [127]. Some naturally occurring flavonoids and several senotherapeutics, especially the tyrosine kinase inhibitors and Bcl-2 inhibitors, which are commonly used to treat cancer, hold therapeutic promise of suppressing viral replication of latently infected HIV cells [50, 51, 128], as well as immunomodulatory effects of reducing proinflammatory mediators [52], leading to abrogation of

neuroinflammation and persistent immune activation associated with HIV infection. By inhibiting CDK9 and Tat transactivation, chrysin, apigenin, and luteolin reinforce HIV latency and induce transcriptional quiescence [51], suggesting a role in silencing HIV reservoirs in humans. Therefore, combining flavonoids with these senotherapeutics could be a viable therapeutic strategy for mitigating ageing, metabolic derangement, and complications associated with HIV treatment. Considering the cost, safety profile, and beneficial effects of polyphenolic flavonoids on various ARDs, research should focus on paving the way for these flavonoids in the clinic as senotherapeutics.

8 Conclusion and Future Perspectives

As cellular senescence is linked to the development and progression of ageing and ARDs, it is imperative to use natural compounds to protect organisms against the effects of excessive accumulation of SC. This review focused on the senotherapeutic effects of flavonoids and their potential mechanisms. Several preclinical shreds of evidence demonstrate that flavonoids can improve cellular senescence by modulating several ageing-associated signalling pathways and cellular protective mechanisms (Fig. 3). The effect of

flavonoids in lowering systemic inflammation and oxidative stress and targeting SCs and their secreted SASP mark their potential as therapeutic agents for senescence.

Ageing and ARDs have a redox-regulated component, which participates actively in the mode of action of several senomorphics. A strategy of specifically targeting the signalling pathways of these redox intermediates of SASP in SCs, such as the redox-sensitive transcription factors NF-κB, Nrf2, or FOXO, instead of the unspecific elimination of ROS, may be a boon for the identification of effective senomorphics in the future. Another factor is the induction of senescence in experimental studies by single stress, whereas, in the physiological state of the organisms, individual cells experience multiple stresses [24]. Therefore, to ensure the reliability of polyphenolic flavonoids on senescence, an approach to mimic the physiological milieu of senescence would be advisable by inducing senescence in cells with various types of stresses. In addition, it is essential to study the effects of these flavonoids in their combined form since they do not exist in plants in isolation.

The bioavailability of polyphenolic flavonoids is generally low due to poor solubility, low permeability, and inferior stability as the liver and intestine metabolize them mostly to glucuronides and sulphates, which severely reduces their
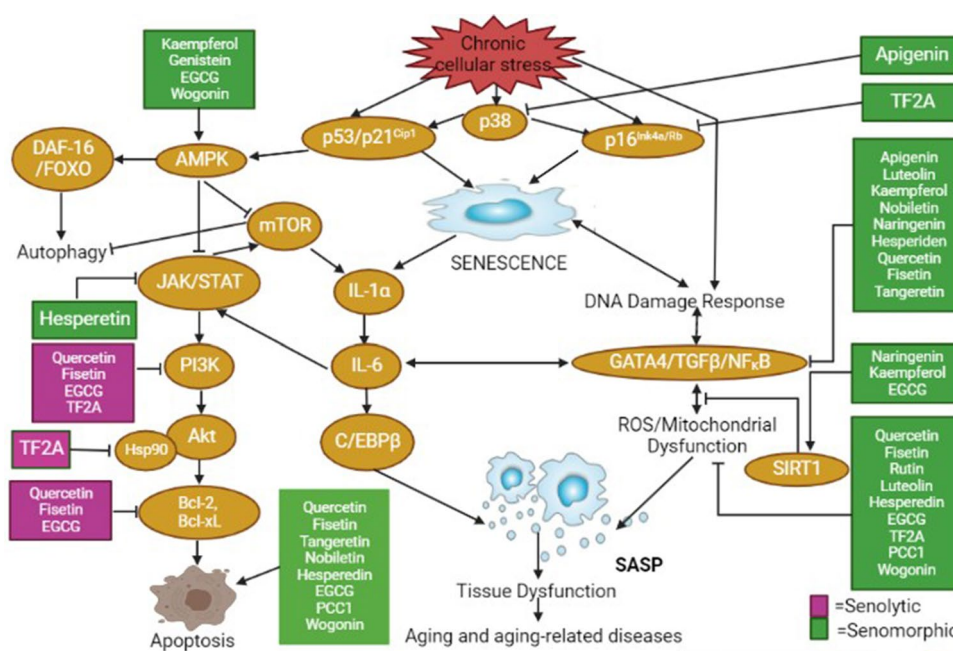

Fig. 3 Model illustrating the potential effects of citrus flavonoids on cellular senescence. Citrus flavonoids are pleotropic molecules that target several pathways including those involved in maintaining SASP, inducing apoptosis of senescent cells by inhibiting pro-senescence pathways or by inhibiting antiapoptotic signalling, in a direct or indirect manner, and activating different cellular protective mechanisms. *AMPK* AMP-activated protein kinase, *Akt* protein kinase-β,

Bcl B-cell lymphoma, *C/EBP β* CAAT/enhancer binding protein, *FOXO* Forkhead box protein, *IL-1R* interleukin-1 alpha, *IL-6R* interleukin-6, *JAK* Janus kinase, *NF-κB* nuclear factor kappa-light-chain enhancer of activated B cells, *PI3K* phosphoinositide 3-kinase, *ROS* reactive oxygen species, *STAT* signal transducer and activator of transcription, *SIRTs* silent information regulators (sirtuins), *TGFβ* transforming growth factor beta. Figure created with BioRender.com

effectiveness as therapeutic agents. Moreover, different people have different genetic predispositions towards the bioavailability of these polyphenolic flavonoids, which might affect the different results for studies with polyphenolic flavonoids. Therefore, it is imperative to develop strategies to abrogate the absorption barriers of these polyphenolic flavonoids, such as co-ingestion with enhancers or other macro- and micro-constituents, improving metabolic stability, structural modifications, and novel delivery systems such as carrier complexes, nanotechnology, and cocrystals. Further studies should be geared toward understanding the interactions between genetic variability and flavonoid bioavailability, which could assist in elucidating the role of genetic factors on polyphenolic flavonoid metabolism.

Furthermore, the multi-target effects of these flavonoids also raise a concern about their potential adverse effects and drug interactions in clinical applications. Therefore, it is vital to determine and match their pharmacokinetic profiles with conventional drugs. However, the specific SC types and SASP targeted by polyphenolic flavonoids could be identified, and the mechanisms of action elucidated using in silico and experimental approaches. Therefore, further studies on specific indications of these flavonoids on SC type and SASP are required, which could be used as templates for designing new leads for combinatory therapy in senescence-associated diseases. There is also the need for large-scale randomized clinical trials to validate the clinical effectiveness of flavonoids as senotherapeutics since much of the information available is from preclinical studies. Flavonoids may be developed as nutraceuticals, food supplements, or complementary and alternative medicines in senotherapeutics and geroprotection.

Declarations

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