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Review article

# The senotherapeutic potential of phytochemicals for age-related intestinal disease

Célia Maria Costa [a], Sílvia Santos Pedrosa [b], James L. Kirkland [c], Flávio Reis [d,e,f], Ana Raquel Madureira [a,*]

[a] Universidade Católica Portuguesa, CBQF—Centro de Biotecnologia e Química Fina—Laboratório Associado, Escola Superior de Biotecnologia, Rua Diogo Botelho 1327, Porto 4169-005, Portugal
[b] Biorbis, Unipessoal LDA, Edifício de Biotecnologia da Universidade Católica Portuguesa, Rua Diogo Botelho 1327, Porto 4169-005, Portugal
[c] Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, USA
[d] Institute of Pharmacology and Experimental Therapeutics & Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra 3004-504, Portugal
[e] Center for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, Coimbra 3000-548, Portugal
[f] Clinical Academic Center of Coimbra, Coimbra 3004-531, Portugal

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ABSTRACT

During the last few decades, life expectancy has increased worldwide along with the prevalence of several age-related diseases. Among aging pathways, cellular senescence and chronic inflammation (or "inflammaging") appear to be connected to gut homeostasis and dysbiosis of the microbiome. Cellular senescence is a state of essentially irreversible cell cycle arrest that occurs in response to stress. Although senescent cells (SC) remain metabolically active, they do not proliferate and can secrete inflammatory and other factors comprising the senescence-associated secretory phenotype (SASP). Accumulation of SCs has been linked to onset of several age-related diseases, in the brain, bones, the gastrointestinal tract, and other organs and tissues. The gut microbiome undergoes substantial changes with aging and is tightly interconnected with either successful (healthy) aging or disease. Senotherapeutic drugs are compounds that can clear senescent cells or modulate the release of SASP factors and hence attenuate the impact of the senescence-associated pro-inflammatory state. Phytochemicals, phenolic compounds and terpenes, which have antioxidant and anti-inflammatory activities, could also be senotherapeutic given their ability to act upon senescence-linked cellular pathways. The aim of this review is to dissect links among the gut microbiome, cellular senescence, inflammaging, and disease, as well as to explore phytochemicals as potential senotherapeutics, focusing on their interactions with gut microbiota. Coordinated targeting of these inter-related processes might unveil new strategies for promoting healthy aging.

## 1. Introduction

Life expectancy has increased worldwide over the past few decades, with current estimates indicating that between 2015 and 2050 the population over 60 years old will double (WHO, 2024). However, with aging multiple debilitating health conditions can arise simultaneously or in rapid succession. Therefore, this demographic shift could create a burden on health and social services. In an attempt to tackle this issue, the United Nations (UN) declared the period of 2021–2030 as the Decade of Healthy Aging. The necessity for academic research to develop strategies to tackle this issue has become imperative.

The biological definition of aging, its causes, and its consequences are somewhat controversial. The World Health Organization (WHO) defines aging as the accumulation of a variety of cellular and molecular types of damage over time, leading to a gradual decrease in physical and mental capacity, a growing risk of disease, and ultimately death (WHO, 2024). Several theories have attempted to explain aging taking into consideration different cellular processes and metabolic pathways including, among others, the mutation accumulation theory, cellular senescence, telomere shortening/dysfunction or oxidative stress, or, from an immunologic perspective, inflammaging (Kirkwood, 2018; Weinert and Timiras, 2003). In recent years, a new interdisciplinary

* Corresponding author.
*E-mail addresses:* s-cmsfcosta@ucp.pt (C.M. Costa), sspedrosa@ucp.pt (S.S. Pedrosa), james.kirkland@cshs.org (J.L. Kirkland), freis@fmed.uc.pt (F. Reis), rmadureira@ucp.pt (A.R. Madureira).

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research field has emerged, Geroscience. This field has a goal of creating novel biologically driven therapeutic and preventive approaches to address core aging mechanisms in order to reduce age-associated multimorbidity and enhance healthspan. The Geroscience Hypothesis postulates that key biological processes/pathways are root cause contributors to the pathophysiology of many age-related and chronic diseases. Therefore, therapeutic approaches that target these fundamental aging pathways could delay, prevent, alleviate, or treat such maladies as a group and consequently have a positive impact on healthspan. While some view aging pathways as specific cellular/molecular targets, others consider broader processes (Campisi et al., 2019). López-Otín, Blasco, Partridge (López-Otín et al., 2013) proposed grouping of fundamental aging mechanisms into clusters: telomere erosion, epigenetic alterations, genomic instability, stem cell exhaustion, cellular senescence, mitochondrial dysfunction, loss of proteostasis, altered cell-to-cell communication, and deregulated nutrient sensing. Moreover, they proposed classification of primary causes of age-related damage, antagonistic responses, and integrative responses. For instance, telomere shortening is a primary cause that leads to cellular senescence, which in turn might induce chronic inflammation (Zhu et al., 2019).

Among the possibilities proposed, the chronic inflammation pathway implies existence of an immunosenescence/inflammaging axis involving a sustained pro-inflammatory state coupled with decreased adaptative immune responses (Santoro et al., 2021). The state of immunosenescence includes the set of changes that take place with aging characterized by a general decline in immune function but impacting primarily adaptative responses. Inflammaging entails a low-grade chronic pro-inflammatory state with chronic stimulation of innate immune responses. These immune changes are closely related to the onset of multiple diseases and reduced healthspan (Fulop et al., 2018). In addition to the overall immune system (IS) decline and accentuated inflammatory state frequently observed with aging, at the cellular level senescence is considered a relevant mechanism. However, although the puzzle is becoming better understood, there are still many parts of this pathway to be explored, including endocrine involvement among others. In response to stress or cellular damage accumulation, cells can either undergo apoptosis, autophagy, or senescence. The mechanisms through which a cell enters one specific pathway and not the others have not been unveiled yet (Dodig et al., 2019). On one hand, cellular senescence is essential for embryonic development, tissue repair, and suppression of tumorigenesis. On the other, accumulation of persisting SCs, as can occur in elderly individuals, contributes to dysfunction of multiple organs (Giaimo and d'Adda di Fagagna, 2012). Senescence can be viewed as essentially irreversible cell cycle arrest that includes the development of a SASP, which can entail the secretion of interleukins, chemokines, growth factors, prostanoids, bradykines, non-coding nucleotides, and other bioactive molecules, which can have autocrine, paracrine, and even endocrine activities that contribute to tissue degeneration, spread of senescence, inflammation, and tumorigenesis. Additionally, increased β-galactosidase activity (SA-β-gal) is often considered a senescence hallmark, however it is important to note that this marker is not exclusive to senescent cells, nor is expressed by all senescent cells (Birch and Gil, 2020; Di Micco et al., 2021; Kumari and Jat, 2021; Tripathi et al., 2021).

Gut homeostasis is fundamental for the overall health of individuals given the pivotal functions exerted by the gut including nutrient and energy absorption/production, barrier protection, and immune priming, among others, together with its close connections to several systems in the human body. Some of these functions and interactions are carried out by a community of microorganisms living in symbiosis with the host. A representative human microbial population resides in the gut (referred as gut microbiota: GM), which has a composition that is unique to individuals but susceptible to variation throughout the lifespan. Among many other factors, aging can be associated with major changes in GM composition that impair the balance between symbiotic and pathogenic communities and reduced microbial diversity, designated as dysbiosis. A correlation between gut dysbiosis and the prevalence of chronic disorders has been observed that suggests interplay between the gut and the IS (Nagpal et al., 2018; Ragonnaud and Biragyn, 2021). Additionally, deterioration of gut barrier function has been speculated to occur with aging, resulting in increased gut permeability as reviewed by Branca, Gulisano, and Nicoletti (Branca et al., 2019). This allows the passage of bacteria, toxins, and inflammatory compounds across the epithelial barrier that exacerbates systemic inflammation and promotes onset of several gastrointestinal (GI) diseases, such as inflammatory bowel disease (IBD). As such, food and microbiota-derived metabolites play a crucial role in gut homeostasis and overall metabolism in elderly people. For example, the abundance of short chain fatty acids (SFCA)-producing bacteria, whose major roles in the host health are well acknowledged, is frequently reduced in older people (Nagpal et al., 2018).

The damaging effects of SCs on adipose, heart, lung, and skin tissues have been reported and there is mounting evidence from pre-clinical studies linking SC accumulation and the SASP to chronic diseases and the geriatric syndromes. As such, it is plausible to infer that SC accumulation in the gut could disrupt homeostasis and contribute to age-related GI diseases (Gasek et al., 2021; Kaur et al., 2020; Ogrodnik et al., 2019; Saccon et al., 2021). However, there is little known regarding the impact of senescence on the gut. Moreover, it is important to explore new therapeutic approaches to either clear or modulate the secretome of SCs.

Several synthetic drugs have shown potential to alleviate the impact of senescence in pre-clinical studies. For instance, dasatinib, navitoclax, or HSP90 inhibitors can eliminate some types of SCs (senolytic effect), while metformin, rapamycin, ruxolitinib, and aspirin can modulate the SASP (senomorphic action) (Fuhrmann-Stroissnigg et al., 2017; Roos et al., 2016; Xu et al., 2015; Zhu et al., 2017; Zhu et al., 2015). However, side-effects could potentially limit use of these agents, prompting research into other alternatives. Interestingly, several classes of phytochemicals, including flavonoids and phenolic acids, have antioxidant and anti-inflammatory properties. Considering that SCs can exacerbate inflammation and promote a pro-oxidant environment, these compounds might represent a viable option for exploring natural product-based senotherapies. In fact, several natural products have shown ability to act upon SCs and their secretome *in vitro* and *in vivo*, such as quercetin, fisetin, curcumin, and procyanidin C1 (Boccardi and Mecocci, 2021; Kim et al., 2019; Xu et al., 2021; Yousefzadeh et al., 2018; Zhu et al., 2017; Zhu et al., 2015).

The aim of this review is to examine the gap between understanding about SC burden and gut homeostasis in age-related GI diseases. Another goal is to explore the potential of phytochemicals to address this through nutraceutical approaches to promote gut health, mitigate age-related changes, and thereby contribute to overall healthy aging.

## 2. Cellular senescence

Cellular senescence, one of the hallmarks of aging, is characterized by essentially permanent cell cycle arrest. As a protective response to stress, cells can enter apoptosis, autophagy, or senescence, although the factors determining which pathway is followed remain to be comprehensively elucidated (Dodig et al., 2019). It has been hypothesized that the chance of a cell becoming senescent depends on the intensity and duration of the trigger, the type of stimulus, and the originating cell type, although fibroblasts and epithelial cells may be more prone to senescence than some other cell types (Abbadie et al., 2017). SCs are subject to immunosurveillance and usually cleared by various innate immune cell types, such as macrophages, T cells, or NK cells as well as some adaptive immune cell subtypes (Di Micco et al., 2021; Prata et al., 2018). SCs are metabolically active, albeit with adaptations. For example, SCs cells exhibit increased resistance to apoptosis, in some cases through up-regulation of the BCL-2 anti-apoptotic family of proteins, and production of SASP factors. Senescent cells are distinct from

quiescent cells. The latter are in a state of reversible cell cycle arrest at the G0 phase, while SC cell cycle arrest is typically at the G1 phase (Kumari and Jat, 2021). Some metabolic adaptations present in quiescent cells also occur in SCs, while others, such as the SASP, are more pronounced in SCs (Terzi et al., 2016).

Cellular senescence is a complex and heterogeneous mechanism comprising distinct phenotypic subsets that depend on the inducer of senescence, cell type becoming senescent, time since induction of senescence, and physiological context (Herranz and Gil, 2018; Kumari and Jat, 2021). Additionally, there are not widely accepted sensitive and specific markers for identifying SCs. Most authors agree on using a multi-biomarker approach for identifying SCs. González-Gualdaet al. (2021) propose a strategy for evaluating senescence *in vitro* by assessing traits including cell-cycle arrest, structural and morphological changes, and specific features related to the SC subtype. Morphologically, SC generally become enlarged and flattened with an increased cytoplasm-to-nucleus ratio. In oncogenic induced senescence, the nucleus becomes prominent, and a typical change of heterochromatin organization can be observed, leading the formation of senescence-associated heterochromatin foci (SAHFs) that are detectible by microcopy, DAPI staining, or other immunohistochemical techniques (Frey et al., 2018; González-Gualda et al., 2021). Expression, protein levels, and/or activities of cell cycle arrest associated cyclin-dependent kinases can occur, such as p16, p53, and/or p21, depending on the senescence inducer and cell type. Senescence also induces metabolic changes, including apoptosis resistance, increased lysosomal content, dysfunctional mitochondria with a partial Warburg shift (from mitochondrial citric acid cycle and oxidative phosphorylation to a less efficient process of anaerobic glycolysis), and SASP factor release. Increased lysosomal content of senescence associated β-galactosidase (SA-β-Gal) and activity at pH 6 can occur in senescence and can easily be detected by histochemical staining (Di Micco et al., 2021; James et al., 2015; Kwon et al., 2019). The SASP is highly variable, but the proinflammatory cytokines IL-6 and IL-8 are frequently present in SCs (Di Micco et al., 2021; González-Gualda et al., 2021). No senescence marker that is fully sensitive or specific for GI tract SCs has been described to date, to our knowledge (Choi et al., 2023).

### 2.1. Inducing factors

Cellular senescence can be induced by such factors as DNA damage, oxidative stress, repeated replication, telomere shortening or dysfunction, oncogenes, radiation, chemotherapeutic agents, mechanical or shear stress, infections, heme proteins, saturated lipids, and many others (Anderson et al., 2019; Di Micco et al., 2021; Ishaq et al., 2022; Kumari and Jat, 2021; Nath et al., 2024; Tripathi et al., 2021). In the case of nuclear DNA damage, a signaling cascade, the DNA damage response (DDR), acts like a checkpoint in cell cycle progression (Wu et al., 2023). Some DDR factors can accumulate at sites of DNA damage, forming DNA repair foci that act to reinforce checkpoint replicative arrest. If such damage persists, the cell enters senescence. Although reactive oxygen species (ROS) are naturally part of mitochondrial metabolism, redox imbalances lead to structural damages in proteins, DNA, and lipids (Juan et al., 2021). Therefore, increased ROS exposure can result in damage accumulation and loss of cellular function, which in turn, contribute to aging phenotypes. Additionally, senescence induced by oxidative stress has been linked to accumulation of dysfunctional mitochondria. It has been proposed that a bidirectional relation exists between nuclear DNA damage and mitochondrial malfunction (Miwa et al., 2022). Telomeric shortening was one of the first senescence inducers described (Zhu et al., 2019). At each cell division, in the absence of telomerase expression, telomeres are reduced in length. Beyond a critical number of kilobase pairs at telomeric ends, the DDR is activated and prompts senescence. However, DNA damage can also be related to telomers, regardless of their length or the shortening that comes with replication. DNA damage can randomly affect the cell genome, including telomeres, and in such case, the DDR cascade is triggered and becomes persistent in telomeres that have suffered damage beyond efficient repair (de Magalhães and Passos, 2018), thus contributing to senescence onset. Oncogenes can be another senescence inducer: oncogenes can be activated by ROS, which trigger a hyperproliferative state, altered DNA replication patterns, and subsequent DNA damage accumulation in fragile regions, such as telomeres (Zhu et al., 2020).

In response to senescence inducers, cells may enter replicative senescence (RS), or stress induced premature senescence (SIPS). When telomeres become critically short, their loss of function induces RS, which represents a senescent state common to several types of somatic cells. SIPS onset is usually related to the above-mentioned oxidative stress or oncogene activation (Kaur and Farr, 2020). Interestingly, DNA damage is a frequent and common inducer of both types of senescence, since telomeres can also suffer damage accumulation and other stressors, often ending up in triggering the DDR. Cell culture models have been developed that can simulate both replicative and stress induced senescence (Bielak-Zmijewska et al., 2014). For example, RS induction can be achieved by isolating cells from old donors or using primary cell lines and subculturing them until their replicative limit is reached. SIPS can be induced in either primary or transformed cell lines by exposing cells to a stressor for a sufficient amount of time (Ott et al., 2018).

### 2.2. Cellular senescence, aging, and disease

Senescence and SASP factor secretion, which can be either beneficial or deleterious, can be viewed as a double-edged sword. Some authors cite this as an example of antagonistic pleiotropy (Giaimo and d'Adda di Fagagna, 2012). For example, cellular senescence is an essential process in embryonic remodeling of transient structures such as the mesonephros and in shaping and function of the placenta (Da Silva-Álvarez et al., 2019). Additionally, senescence can play a role in tissue repair or wound healing processes (Wilkinson and Hardman, 2020). Finally, senescence is a key mechanism for tumor suppression by limiting the proliferation of damaged cells through up-regulation of the p53, p16, and p21 pathways (Dodig et al., 2019). On the other hand, with aging, accumulation of SCs, probably because of an IS that fails to eliminate them and through the secretion of SASP factors, a pro-inflammatory environment arises. This in turn, supports tumor development and has been correlated with several age-related diseases, geriatric syndromes, and other conditions characterized by accelerated aging such as diabetes, lung disease, atherosclerosis, and GI diseases, among others (Kumari and Jat, 2021). Several authors have pointed to a potential a causal link between the accumulation of SCs and deterioration/loss of function of several tissues (Wilkinson and Hardman, 2020). This has also been shown in pre-clinical studies, in which clearance of SCs resulted in the alleviation of multiple age-related phenotypes (Pignolo et al., 2020). Extensive research, mainly in mice, has established a causal relation between senescence and several diseases including osteoporosis, frailty, cardiovascular disease, pulmonary fibrosis, renal disease, neurodegenerative diseases, hepatic steatosis, metabolic dysfunction, and osteoarthritis. For comprehensive and detailed information about existing evidence that links senescent cell burden to each one of the diseases above mentioned, readers are encouraged to consult several recent reviews (Kaur and Farr, 2020; Palmer et al., 2022; Pignolo et al., 2020; Suda et al., 2023;Tchkonia et al., 2021;Wyles et al., 2022).

In sum, cellular senescence is a critical biological process characterized by essentially permanent cell cycle arrest in response to stressors such as DNA damage and oxidative stress. While senescence has beneficial roles in development, tissue repair, and cancer prevention, the accumulation of persistent SCs with age can contribute to chronic inflammation and age-related diseases. Identifying and targeting these cells through emerging therapies holds promise for mitigating the negative impact of aging and improving overall health.

## 3. Age-related changes in the gut

### 3.1. Variation of gut microbiota composition throughout life

The GM includes a community of millions of commensal microorganisms in close interplay with the human host and has even been labelled by some authors as an organism *per se*. The GM comprises several types of microorganisms, including bacteria, viruses, *Archea*, and unicellular Eukaryotes. The bacterial community, the most prevalent of these types of microorganisms, represents almost 98 % of the total microbiota, belonging to 4 main phyla: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*. There is a commensal relation between GM and the human host that it is mutually beneficial and mainly mediated by the metabolites produced. For example, the microbiome plays a key role in food digestion and nutrient absorption since the GM ferments undigestible fibers, producing SCFA. These are mostly absorbed by colonocytes and used by them as a source of energy and mucin production or are further transported into the blood stream to other tissues where they exert a diversity of effects, including contribution to regulation of metabolism of carbohydrates and lipids, among other functions (Cătoi et al., 2020; Ragonnaud and Biragyn, 2021).

Microbial colonization starts after birth and it is highly dependent on the form of delivery (*e.g.*, natural childbirth *vs*. *Caesarian* section), ethnicity, nutrition, immunological stimuli, and other environmental factors. However, during early life the GM has a simple structure with dominance of *Bifidobacterium*. As time passes, complexity increases, begins to stabilize at around 12 years of age and then remains stable through mid-adulthood. At older ages, GM undergoes several changes. While it is difficult to specify a cause-and-effect relationship between these changes and aging due to the lack of longitudinal or interventional human studies, some tentative conclusions have been drawn. For example, progeroid mice that received fecal microbiota transplants from wild-type mice lived longer than those that did not (Wang et al., 2021). Furthermore, progeroid mice, which also received fecal microbiota transplants coupled with *Akkermansia muciniphila*, exhibited increased lifespan compared to untreated progeroid mice (Narasimhan et al., 2021). This hints at a correlation between GM and longevity. While general differences at the species level are hard to point out, there are changes at the phylum level that can be identified, such as an increased prevalence of *Firmicutes* and *Proteobacteria* and reduced abundance of *Bacteroidetes*. Moreover, potential pro-inflammatory pathobionts have been reported to become more abundant, namely *Enterobacteria*, *Streptococci*, and *Staphylococci* (Askarova et al., 2020). Other authors view such GM composition alterations as a rearrangement with increased abundance of subdominant species. In the context of gut microbiota, the concept of α-diversity is highly relevant as it refers to the variety (richness) and abundance (evenness) of microbial species in a given environment. Reduced α-diversity it is often observed among older and frail individuals, usually linked to dysbiosis, cognitive impairment and to inflammatory pathologies (Badal et al., 2020). Furthermore, there is increasing evidence for transmission of microbiota among individuals living within the same social groups (Ragonnaud and Biragyn, 2021). Recently, not only similarities have been observed between the GM composition of individuals living in nursing facilities, but also a general pattern of increased abundance of inflammatory and pathogenic species and an increased prevalence of dysbiosis after 1 year of residency across nursing homes (Haran et al., 2021). In contrast, the microbiota of centenarians, often considered examples of successful aging, is distinct from the microbiota of the general population of elderly individuals. For example, although *Firmicutes* remains a dominant phylum, there is a loss of diversity, in particular reduced contribution of *Clostridium* cluster XIVa and a rearrangement of *Clostridium* cluster IV. Additionally, centenarians have higher abundance of *Proteobacteria*, which includes several pathobiontic bacteria; however, there is an increased abundance of butyrate-producing bacteria (Cătoi et al., 2020).

Dysbiosis is often defined as major changes or imbalances in the microbial community structure. When these changes are age-related, they usually occur together with immune impairment and comorbidities. The intestinal epithelium has a high cellular turn-over and is usually regenerated every three to five days due to the stem cells present in the crypts. This is a tissue highly sensitive to DNA damage. As cells move upward, they undergo apoptosis and are shed into the intestinal lumen. With aging, the gut structure also undergoes several changes, impacting the integrity of the epithelial barrier, its regenerative capacity, mucus layer composition, and peristalsis. Additionally, the aging gut has increased crypt and villus sizes, reduced number of crypts, and changes in cell composition such as abundance of Paneth cells (secretory cells that release antimicrobial peptides and other components important for host defense) and goblet cells (which produce mucus), and stem cells, indicating impaired intestinal crypt regenerative function. This usually results in a leaky gut, with reduced cellular turnover. This allows the passage of microbiota-derived metabolites which in turn contribute to systemic age-related inflammation, *i.e.* inflammaging (Bosco and Noti, 2021; Nalapareddy et al., 2022).

### 3.2. GM, aging, immunosenescence, and inflammaging

The relation between GM, aging, immunosenescence, inflammaging, and onset of disease represents "circular causality", since determining which of these mechanisms represents a cause or consequence is challenging. As mentioned above, inflammaging is one of the pillars of aging that is connected to the concept of immunosenescence, although how inflammaging relates to immunosenescence has not been fully elucidated (Fulop et al., 2018; Santoro et al., 2021). The state of immunosenescence can be defined as a global decline in immune function affecting mainly the adaptative response. During this process, subsets of immune cells such as T cells appear to become senescent. Inflammaging is linked to chronic stimulation of the innate immune response. From an evolutionary standpoint, age-related changes in the IS can be considered a response to challenges (Fulop et al., 2018; Santoro et al., 2021). The fact that a high percentage of the elderly have age-related conditions suggests a maladaptation, or an imbalance, in which inflammation plays a detrimental role. In contrast, long-lived individuals who are effectively a model of successful aging may have been able to adapt to challenges and retain a properly balanced immune response and therefore onset of diseases is delayed or mitigated (Fulop et al., 2018). Many factors can contribute to inflammaging including immunosenescence, oxidative stress, accumulation of age-related cell debris and decreased disposal ability, telomere shortening and nuclear DNA damage. Other factors are excess energy or nutrients, genetic predisposition, SASP factors released by SCs, and translocation of proinflammatory bacterial products across the epithelial barrier through a leaky gut, among others (Campisi et al., 2019; Santoro et al., 2021). Narasimhan et al. (2021) have suggested that inflammaging, which might induce systemic inflammation, derives from senescent cells, gut dysbiosis, and leaky gut (Fig. 1.). Some also consider GM age-related changes to be triggers of inflammaging (Fernandes et al., 2019; Santoro et al., 2021; Santoro et al., 2020). Gut-derived inflammation might be related to the presence of a wide range of pattern-recognition receptors throughout the GI tract that ensure constant communication with the overall IS through local mesenteric lymph nodes (Nagpal et al., 2018). Therefore, targeting chronic inflammation pathways and its gut-related inducers might constitute a valuable strategy to prevent or alleviate age-related diseases.

### 3.3. Senescence, gut metabolites, and intestinal disease

Microbiota-derived metabolites are key players in gut homeostasis and disease. They are usually divided into diet-derived metabolites (*i.e.* SCFA, indole derivatives), metabolites synthetized *de novo* (such as polysaccharide A, polyamines, bacterial vitamins), and metabolites generated by the host but modified by the GM, such as secondary bile

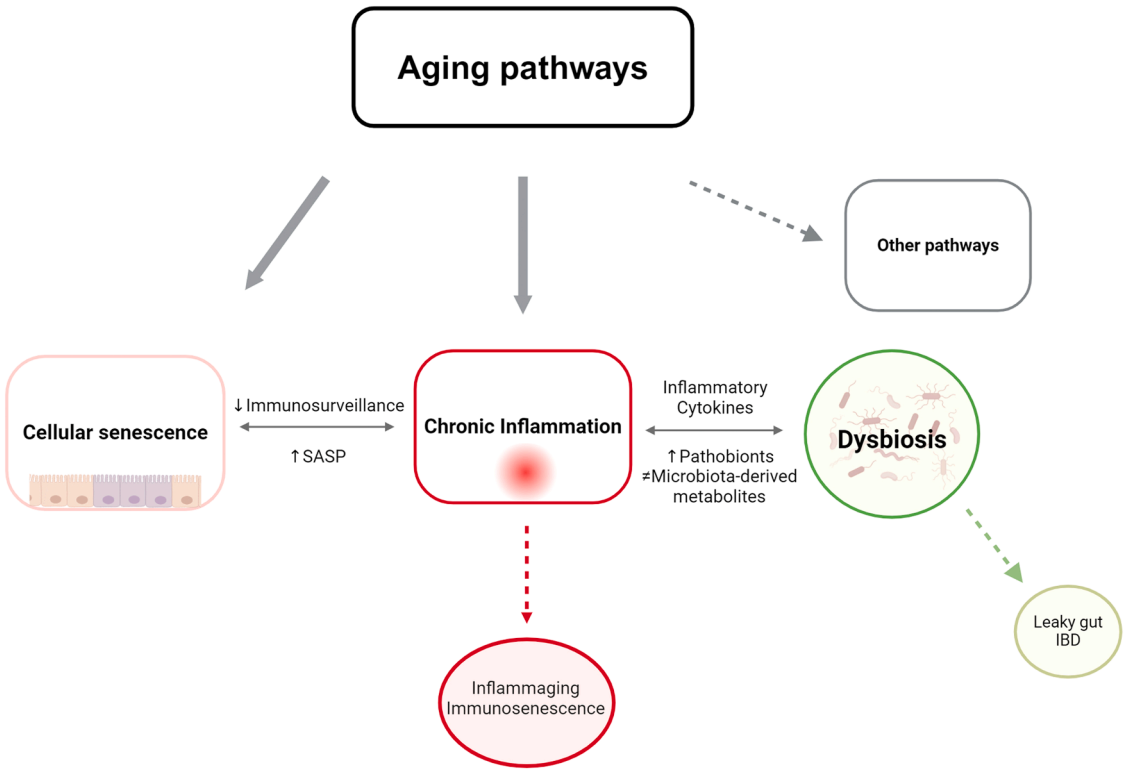


**Fig. 1.** Schematic view of the relation between cellular senescence, chronic inflammation, the gut, and its microbiota.

acids (Agus et al., 2021; Liu et al., 2022; Wu et al., 2021). A full description of the potential benefits of these metabolites is beyond the scope of this review. Readers may refer to comprehensive reviews, such as Liu et al. (2022). Indeed, the GM is able to produce a large number of bioactive metabolites, an area that remains largely unexplored. Among them, SCFA (acetate, butyrate, and propionate) bear mention, as they are the most studied class of metabolites and are reported to exert a wide array of benefits for gut homeostasis, which include among others: maintaining a reduced luminal pH value, promoting growth of beneficial bacteria, regulating mucus production (which helps in the maintenance of the intestinal barrier), and positively influencing overall metabolism (Silva et al., 2020). These SCFAs are absorbed by colonocytes and used as an energy source, while remaining fatty acids enter the circulatory system and reach other tissues and organs. Among many functions, propionate and acetate act as liver substrates contributing to gluconeogenesis and lipogenesis, respectively. Butyrate can act locally to exert anticarcinogenic effects by inhibiting histone deacetylases and associated signaling pathways, thereby suppressing colorectal cancer cell proliferation. However, the concentration of SCFAs and other beneficial metabolites in the gut decreases with age, perhaps because of changes in GM composition and preferred metabolic pathways, from saccharolytic to proteolytic metabolism (Askarova et al., 2020; Cătoi et al., 2020). Furthermore, these shifts may benefit pathobionts—opportunistic microbes that emerge due to disturbances in the healthy microbiome and whose proliferation can lead to disease. This interference with intestinal barrier function may activate pro-inflammatory pathways, contributing to the onset of inflammatory diseases such as IBD. This group of diseases that includes ulcerative colitis and Crohn's disease has been increasing among older patients, although not being currently classified as age-related diseases (Faye and Colombel, 2022). This trend may be due to the relatively low mortality associated with these diseases, coupled with stable incidence in the general population, resulting in a growing number of older individuals with these conditions. It is interesting to consider how they might interact with the aging immune system. Older patients with IBD will likely experience the natural accumulation of senescent cells that accompanies biological aging. Although only correlations have been established, inflammation, telomere dysfunction, senescence, and IBD act through interconnected pathways. For example, patients with Crohn's Disease have increased expression of cellular senescence molecular markers (p21 and p16) and telomeric changes, which might be connected to the disease progression and mucosal inflammation (Faye and Colombel, 2022; Hold et al., 2014; Sienkiewicz et al., 2023; Tchkonia and Kirkland, 2018; Wyles et al., 2022).

While cellular senescence might constitute an important process in IBD by controlling cellular proliferation, continuous exposure to SASP factors further exacerbates inflammation. It has been hypothesized that macrophages, which can be recruited to clear senescent cells in damaged tissues, are unable to do so, due to decreased recruitment and macrophage damage (Prata et al., 2018). Hence, there can be accumulation of SCs, which in turn further exacerbates inflammation. Moreover, older patients with IBD have reduced life-span and increased risk of developing other age-related conditions such as diabetes, cardiovascular diseases, or dementia (Sienkiewicz et al., 2023). The relation of the GM and its metabolites to the pathogenesis of IBD cannot be overlooked. The GM in patients with IBD has reduced diversity accompanied by alterations in the prevalence of specific taxa, resulting in a shift in community structure (Alshehri et al., 2021; Vestergaard et al., 2024). At the level of phyla, the proportion of *Firmicutes* and *Bacteroidetes* is reduced, while the proportion of *Proteobacteria* and *Actinobacteria* is increased. Additionally, beneficial bacteria such as *Faecalibacterium prausnitzii*, *Clostridium spp.*, and *Bacteroidetes fragilis* appear to have reduced abundance. This results in reduced production of SCFA as well as of mucin and antimicrobial peptides, together with dysregulation of tight junction proteins. In parallel, potential pathobionts belonging to *Enterobacteriaceae* (*i.e.* aggregative and invasive *E. coli* and $H_2S$ producers) become more prevalent and are translocated (Baldelli et al., 2021; Lavelle and Sokol, 2020). Interestingly, this scenario is more prominent in Crohn's disease than in ulcerative colitis (Sultan et al., 2021).

Hence, age-related changes in the gut microbiota significantly

impact health, contributing to conditions including inflammaging and immunosenescence. The composition of the GM evolves throughout life, stabilizing in adulthood but becoming less diverse with age, often leading to dysbiosis. This imbalance is associated with increased inflammation and susceptibility to age-related diseases. The presence of beneficial metabolites such as SCFA decreases while pro-inflammatory species become more prevalent. These changes compromise gut integrity, promote systemic inflammation, and are linked to diseases such as IBD. Understanding and targeting these age-related gut changes may help mitigate their negative health impact.

## 4. Phytochemicals as senotherapeutic compounds

### 4.1. Senotherapeutics: synthetic and natural compounds

Senotherapies have gained increased relevance and can be classified according to their underlying mechanism of action as senolytics or senomorphics. Senolytics are agents that can selectively induce apoptosis in SCs through targeting enzymes related to pro-survival and anti-apoptotic pathways. The most cited mechanisms rely on targeting ephrin-dependent Src kinases, BCL-2, or HSP90 (family of chaperone proteins related to cell proliferation) or compounds that target the p53 or p21 pathways (Fuhrmann-Stroissnigg et al., 2017; Roos et al., 2016; Wissler Gerdes et al., 2020; Zhu et al., 2015). Another recent innovative strategy regarding senolytics is a potential nutraceutical approach using galactose-coated nanoparticles loaded with cytotoxic drugs, which able to selectively target senescent cells due to the increased amount and activity of SA-β-Gal (Di Micco et al., 2021). Across the literature, an array of senolytic compounds has been identified together with the mechanisms through which they target and clear SCs, however, the most established senolytics are dasatinib, quercetin, and fisetin (Zhang et al., 2023).

Recent preclinical trials with animals treated with dasatinib have shown improvements in metabolic function and adipose tissue (Islam et al., 2023). Other studies showed that older animals treated with dasatinib+quercetin had alleviation of inflammaging, which is often characterized by exacerbated senescence markers and increased abundance of certain circulating or adipose-tissue resident immune cells (Ruggiero et al., 2023). Dasatinib, either alone or in combination with quercetin, has been validated in phase I and II clinical trials as a safe and effective approach that tackles specific aspects of diabetic kidney disease (Hickson et al., 2019), idiopathic pulmonary fibrosis (Justice et al., 2019), and Alzheimer's disease (Gonzales et al., 2023). Fisetin, a natural flavonoid, has been explored as a senolytic in ongoing phase II clinical trials regarding its ability to attenuate inflammation and frailty (NCT03675724 and NCT03430037) and ameliorate skeletal health (NCT04313634) (Chaib et al., 2022). As opposed to senolytics, senomorphics act by inhibiting SASP factor production at the transcriptional level or by neutralizing the effects of secreted SASP factors (Zhang et al., 2023). These compounds can target pathways related to release of SASP factors (mTOR, JAK/STAT pathways, p38MAPK, among others), transcription factors that regulate SASP genes (*e.g.*, NF-κB), or specific neutralizing antibodies against SASP factors such as IL6, IL8, IL1α, or TNF-α (Di Micco et al., 2021; Kaur et al., 2020; Lagoumtzi and Chondrogianni, 2021). In this class of compounds, metformin, rapamycin, and ruxolitinib are among the most prominent. Metformin, a drug for treating type 2 diabetes mellitus, exhibits promising results as a geroprotector. In fact, epidemiological studies demonstrated a reduced incidence of age-related diseases and reduced overall mortality in both diabetics and non-diabetics. A number of *in vitro* and *in vivo* preclinical studies suggest metformin might tackle several aging hallmarks, including cellular senescence, through downregulating pro-inflammatory cytokines, NF-κB signaling, and activating Nrf2-Gpx7 (Kulkarni et al., 2020). Rapamycin, a mTOR inhibitor, initially found to be an anti-fungal compound, was recognized as an immunosuppressive and anti-proliferative agent (Suto and Karonitsch, 2020; Wang and Eisen, 2022). More recently, preclinical trials in cell lines and animal models suggest it may increase lifespan, at least under conditions in which environmental perturbations are minimized, reduces SC burden, and attenuates the SASP (Wang et al., 2017; Zhang et al., 2023). Perhaps senolytics have an advantage over senomorphics, since clearing SCs represents a definitive solution instead of continuously administering SASP inhibitors. However, this is not clear since side effects of complete and/or prolonged clearance of SCs have not been explored (Di Micco et al., 2021). Additionally, such drugs need to precisely target SCs and induce its apoptosis.

Synthetic senotherapeutic compounds raise questions regarding systemic effects and intrinsic dose-dependent toxicity (Kaur et al., 2020). For instance, navitoclax, another senolytic agent, causes hematological toxicity (González-Gualda et al., 2020). On the other hand, many phytochemicals have antioxidant and anti-inflammatory activities that hint at potential senolytic or senomorphic effects (Zhang et al., 2023). However, natural compounds can have multiple targets and interactions above and beyond any selective action on SCs (Zhang et al., 2023). This points to the increasing relevance of exploring phytochemicals as senotherapeutics given their broad mechanism of action and systemic effects.

### 4.2. Phytomolecules as potential senolytics/senomorphics

The concept of geroprotectors has emerged but without consensus across the scientific community regarding definitions or criteria. However, there is some agreement that a geroprotector should attenuate molecular, cellular, or physiological aging hallmarks, such as cellular senescence, with a goal of increasing healthspan (Moskalev, 2023; Schork et al., 2022). Geroprotectors can be compounds with antioxidant, antidiabetic, immunomodulating activity (Moskalev et al., 2017). Interestingly, molecules with anti-inflammatory and antioxidant activity are more likely to display senotherapeutic activity through suppressing senescence or by modulating the SASP due to overlapping pathways (Zhang et al., 2023).

Historically, plant-derived products have been a primary source of medicine, being used for thousands of years in traditional Chinese medicine. Despite the rise of synthetic and microbial-based drugs, plant-based compounds continue to offer significant bioactive potential (Islam et al., 2021; Xiao and Bai, 2019). Phytomolecules, namely plant secondary metabolites, have been extensively studied for their impact on biochemical processes and they exhibit interesting bioactive potential. These compounds are structurally diverse and can classified as phenolic compounds, phytosterols, terpenes, and N-containing and S-containing compounds, which in turn are further divided into sub-classes (Twaij and Hasan, 2022; Wang et al., 2022). Phenolic compounds (PC), one of the most studied classes of plant metabolites, can be sub-divided into phenolic acids, flavonoids, stilbenes, lignans, and tannins (Fig. 2). They are abundant in vegetables, fruits, and cereals and are present in a well-balanced diet (Direito et al., 2021). Long-term deficiency of PC has been correlated with increased risk of type 2 diabetes, gastrointestinal problems, neurodegenerative diseases, and even certain cancers (Cory et al., 2018; Kasprzak-Drozd et al., 2021). However, accurately determining effects of PC in humans are challenging for several reasons, including highly variable dietary intake, associated dietary habits, differing PC content across foods, PC interactions with food matrix, and effects of PCs on metabolism, which is variable among individuals (Eseberri et al., 2022; Kasprzak-Drozd et al., 2021). However, through epidemiological studies, it has been possible to find correlations between ingestion of polyphenol-rich foods and disease prevention (Scalbert et al., 2005). Regardless of the unequivocal antioxidant, anti-inflammatory, antimicrobial, and antitumoral potential of PC, therapeutic applications have been limited due to the poor bioavailability (Albuquerque et al., 2021; Kasprzak-Drozd et al., 2021). Despite terpenes representing the largest and most diverse class of plant secondary metabolites, they have been less studied considering their

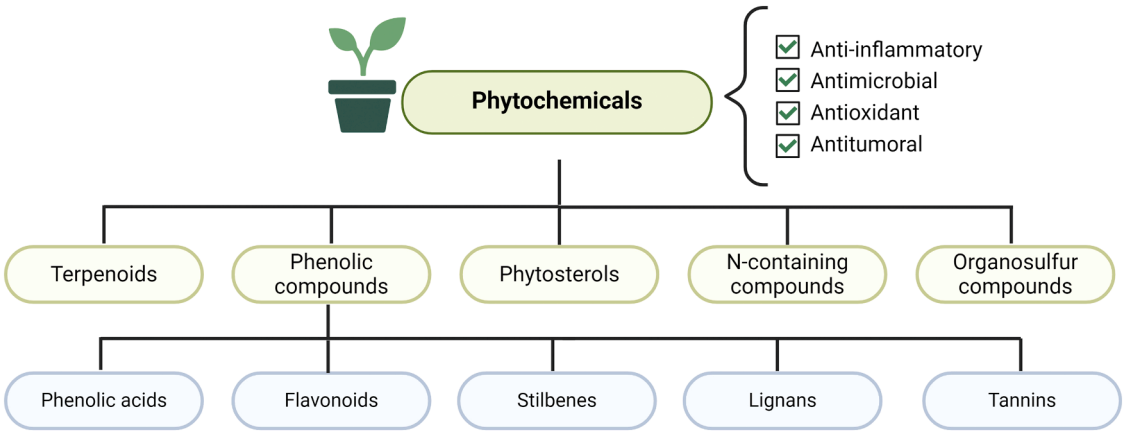


**Fig. 2.** Schematic view of the different classes of phytochemicals and the most common bioactive properties associated with them.

potential to be natural geroprotectors (Proshkina et al., 2020). Terpenes are classified according to the number of carbon units they have: monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, or poly-terpenes. These compounds and their derivatives have potential importance in healthcare and for the pharmaceutical industry, being relevant for cosmetics and skin applications, including their use in formulations such as ointments or creams to attenuate itching or pain (Jahangeer et al., 2021). This class of phytochemicals has demonstrated bioactive potential through *in vitro* and *in vivo* studies, as anti-inflammatory, anti-tumoral, antioxidant, antibacterial, anti-fungal, anti-viral, anti-parasitic, anti-coagulant analgesic, and sedative agents (Rodríguez and Johnson, 2023). Some terpenes have poor solubility and bioavailability and are unstable, and in some cases, volatile.

Phenolics have also been explored for ability to influence GM composition and the gut epithelium. An example of the effect of PC on the GM is the prebiotic-like effect on *Akkermansia muciniphila* (Alves-Santos et al., 2020). The influence of PC upon the GM is not generalized: many effects are specific for each PC. Additionally, phenolics also have anti-microbial properties, which might be the mechanism of action by which other beneficial bacteria are increased in abundance. Other reports suggest that phenolics may contribute to an overall increase in GM diversity (Farràs et al., 2020). The bioconversion of PC by the GM represents another dimension of this interplay and influences the bioavailability and efficacy of these compounds (Santino et al., 2017). These phytochemicals can also tackle intestinal inflammation through the NF-κB pathway, as demonstrated in preclinical studies (Laurindo et al., 2023). Moreover, PC can positively contribute to maintenance of intestinal barrier function by upregulating junctional proteins (Sandoval-Ramírez et al., 2021). Others report that PC can activate AMPK, which controls epithelial permeability and inflammatory signals, contributing to the intestinal homeostasis (Domínguez-Avila et al., 2021). From a cellular point of view, PC can affect signal transduction pathways, which in turn can influence several cellular processes such as proliferation, apoptosis, differentiation, and redox balance, among others. Additionally, PC can upregulate tumor suppressor genes, induce cell cycle arrest, and even model NF-κB (a transcription factor related to immune responses) and NrF2 activation (a transcription factor related to antioxidant responses (Direito et al., 2021; Fakhri et al., 2022). For example, fisetin is a naturally occurring flavonoid with recognized anti-inflammatory, antioxidant, antibacterial, and anti-carcinogenic activities (Ravula et al., 2021). Additionally, it is a potential senolytic since it can selectively trigger apoptosis through the BCL-2 pathway (Partridge et al., 2020; Yousefzadeh et al., 2018; Zhu et al., 2017).

### 4.3. *Phytomolecules as nutraceuticals for intestinal disorders*

PCs' ability to influence cellular processes related to senescence, reduce inflammation, and enhance GM composition suggests its potential as a senotherapeutic. This could make PC valuable for targeting senescence and managing gut inflammation-related diseases, such as IBD. For example, quercetin is a flavonoid considered to be a powerful antioxidant and a senolytic that inhibits anti-apoptotic genes and pathways in senescent cells. Additionally, it is, along with curcumin and resveratrol, a compound with reported efficacy and safety in animal models of colitis (Martin and Bolling, 2015). Several other compounds, including green tea catechins, and olive derived polyphenols, also exhibit senotherapeutic potential and also ability to alleviate IBD-related inflammation (H Farzaei et al., 2015; Sharma, 2021; Yousefzadeh et al., 2018; Zhang et al., 2023). Nevertheless, it is important to point out that the efficacy of these compounds is weak, and some mechanisms of action are not fully understood.

Terpenes might also have potential for treating intestinal inflammation. Although no clinical trials have been performed that we are aware of, preliminary studies point towards the potential of carnosic acid, glycyrrhizin, compound K, and oleuropein due to their safety and immunomodulatory potential (Rodríguez and Johnson, 2023). Araruna, Serafim, Alves Junior et al. (Araruna et al., 2020) reviewed twelve terpenes regarding anti-inflammatory activity in *in vitro* and *in vivo* models with respect to potential to tackle IBD and reinforced the notion that terpenes have anti-inflammatory activity through a broad range of pathways. For example, while geraniol and oleanolic acid block the release of inflammatory cytokines and inhibit NF-κB, D-limonene and thymol suppress MAPK signaling pathways. Terpenes can also contribute to gut homeostasis by positively modulating GM composition. For example, carnosic acid can reduce inflammation in a colitis mouse model and also suppresses growth of potential pathogens (Du et al., 2023). Ginsenoside Rk3 increases bacterial diversity and promotes growth of probiotic bacteria (Bai et al., 2021). Furthermore, due to their properties, terpenes might be geroprotectors. Proshkina et al. (2020) methodically reviewed a number of terpenes according to various criteria that suggest a compound may be geroprotective (stress resistance, toxicity, lifespan extension, aging biomarkers, among others) and concluded that most classes of terpenes include compounds with geroprotective potential, including against senescence. For example, fucoxanthin exhibited a protective effect against senescence in human fibroblasts, ginsenoside and lupeol downregulated senescence markers, including β-SA-Gal, p16, p21, and p53, and camphor displayed ability to attenuate cellular senescence (Liu et al., 2021; Song et al., 2014).

Overall, comprehensive examination of studies investigating the effects of these compounds reveals similarities in the pathways targeted to alleviate intestinal inflammation and those implicated in cellular

senescence, particularly those related to inflammatory cytokines. Table 1 summarizes key studies investigating the effects of phenolic compounds and terpenes on gut-related disorders and cellular senescence pathways. This table highlights the multifaceted actions of these phytochemicals, including their anti-inflammatory, antioxidant, and anti-senescence properties, reinforcing the notion that compounds with anti-inflammatory and antioxidant potential may have senotherapeutic potential.

Dietary phytochemicals might directly affect or be further metabolized by the GM. Polyphenols represent a classic example of this phenomenon since they can exert a prebiotic effect on GM or might be biotransformed by gut microorganisms (Gadecka and Bielak-Zmijewska, 2019). Polyphenols are hydrolyzed by lactase-phlorizin hydrolase, an enzyme present in the brush border of small intestine epithelial cells, into aglycones and are absorbed by passive diffusion. However, polyphenols are generally poorly absorbed, and most reach the colon unaltered. Once in the colon, the GM enzymes can catalyze hydrolysis, cleavage, or reduction reactions. The polyphenols are conjugated into metabolites and more easily absorbed (Davinelli and Scapagnini, 2022; Wu et al., 2021). Nevertheless, biotransformation reactions are highly variable and difficult to predict or categorize given that they depend on the type of phytochemical and on GM composition. This variability results in a myriad of consequences, as phytochemicals may be broken down by the GM into small molecules with entirely different bioactivity than the original molecule. Furthermore, these bioconversions might result in compounds either less or more toxic than the original one. For example, administration of carnosic acid in a mouse model of IBD, in addition to the effects on inflammation and in the GM composition, resulted in altered fecal metabolomic profiles, which promoted glutamine-glutamate and tryptophan metabolism (Du et al., 2023). Another example is the hydrolysis of amygdalin by GM into toxic cyanide, although this does not cause poisoning. In contrast, aconite, an alkaloid that is potentially neurotoxic, is transformed by GM into compounds with reduced intestinal absorption (Wang et al., 2022).

Altogether, the anti-inflammatory, antioxidant, and anti-tumoral activities common to several classes of phytochemicals hint for their potential senotherapeutic effect. In fact, the pathways targeted by phytochemicals often overlap with those altered in cellular senescence and in IBD. Moreover, in addition to the acknowledged beneficial effects of several molecules *per se*, particularly concerning SCs and gut homeostasis, the metabolism of these phytochemicals by GM is also worth exploring, given the bioactive potential they encompass.

## 5. Future perspectives

The study of cellular senescence remains a field of study highly relevant to geroscience (Gasek et al., 2021). However, SC populations are highly heterogenous since there are distinct types of senescence and these cells do not acquire the same features, including their secretome, metabolism, and phenotype across different human tissues. While senescence in fibroblasts has been extensively studied, there is a lack of studies about senescence in tissues associated with the GI tract, particularly the intestine. For example, it is important to understand in detail how senescence affects the gut, namely, which cells contribute the most to senescent cell burden and SASP release, given the high cellular turnover of gut epithelium. As such, it would be interesting to explore intestinal senescence and investigate novel hallmarks specific to these tissues. It would be useful to simulate senescence *in vitro*, either replicative or stress induced, and fully characterize senescence hallmarks in different cell types through cell culture models of increasingly complexity. Additionally, these kinds of studies could also lay the foundation for standardized models of senescence in the gut, with delineation of criteria that would be useful for screening new senotherapeutics. From a complementary perspective, it has been shown that accumulation of SC and continuous release of SASP factors impacts the onset of several diseases across various tissues (bone, brain, muscle, *etc*.). Hence, it is reasonable to infer that SCs and their SASP might be a contributing factor to gut inflammation and dysbiosis, which in turn plays a role in diseases such as IBD. However, this potential link between senescence and chronic gut inflammation remains poorly explored.

Phytochemicals encompass a realm of bioactivities that have been studied extensively. Among them, PC and terpenes have been specifically explored as geroprotectors due to their anti-inflammatory and antioxidant potentials, which attenuate many age-related comorbidities. A single compound might exert these effects through several pathways. These pathways can overlap with those involved in onset of senescence. Therefore, it would be pertinent to explore these phytochemicals as senotherapeutics and elucidate the pathways involved. Only then may phytochemicals serve as an alternative to synthetic senotherapeutics, some of which can have serious side effects. However, the poor bioavailability of phytochemicals may hinder their efficacy. Furthermore, their interactions with the GM through bioconversion reactions might alter both bioavailability and even their biopotential. Given the large numbers of PC and terpenes, it is difficult to predict and/or categorize the intestinal metabolites formed as a result of their metabolism. Therefore, it is key to delineate two aspects of phytochemicals (preferably in animal models): the intestinal metabolites generated and the impact of targeted release of these compounds using delivery systems that ensure they reach the colon and maintain bioactivity.

## 6. Conclusions

There is a clear link between age-related senescence and the onset of disease. Moreover, gut hemostasis, by governing GM composition and inflammation, appears to be heavily involved in aging, either in disease or successful (healthy) aging. An emerging relation between cellular senescence and GM has become increasingly relevant in such a way that age-related alterations in the structure of the intestinal epithelium could be caused by gut dysbiosis, which in turn leads to conditions such as leaky gut. Gut microbiota-derived metabolites can add to inflammation induced by the SASP, either locally or even systemically. In contrast, these compounds also have the potential to suppress the SASP, tackling senescence and its deleterious effects. In parallel, phytochemicals may be geroprotectors with potential to address several aging pathways, among them, their impact on cellular senescence with parallel positive effects on the GM. This might unveil a new strategy for maintaining a healthy GM though phytochemical supplementation as an approach to prevent SC accumulation, inflammation, and ultimately diseases that can impede healthy aging.

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## CRediT authorship contribution statement

**Célia Maria Costa**: conceptualization, writing original draft, writing (review and editing); **Sílvia Pedrosa**: conceptualization, supervision, writing (review and editing); **James L. Kirkland:** conceptualization, supervision, writing (review and editing); **Flávio Reis**: conceptualization, supervision, writing (review and editing). **Ana Raquel Madureira**: conceptualization, supervision, writing (review and editing).

**Table 1**
Overview of studies focused on the effects of phenolic compounds and terpenes on gut-related disorders and senescence pathways.

| Compound | Type of study | Senescence pathways targeted | Gut-related effects | Main outcomes | References |
|---|---|---|---|---|---|
| **Apigenin** | Pre-clinical *in vitro* study with human bone marrow stromal stem cells (hBMSCs) | -↓SA-β-Gal<br>-↓expression of p16, p21, and p53<br>-↓expression of SASP related genes | | Apigenin enhanced osteoblastic differentiation of hBMSCs and reduced the burden of cellular senescence and inflammation | Ali et al. (2024) |
| | Pre-clinical animal model- colitis mouse model | | -↓expression of pro-inflammatory cytokines (TNF-α, IL−1β, IL6)<br>-↑expression of anti-inflammatory cytokines including IL10.<br>-↑expression of tight junction proteins<br>-↑abundance of *Akkermansia* and SCFA | Apigenin alleviated induced UC by balancing gut microbiome, inhibiting inflammation and improving gut barrier function | Fu et al. (2022) |
| **Fisetin** | Pre-clinical animal model-mouse | -↓expression of p53, Bcl2 | -↑abundance of *Akkermansia muciniphila* | Fisetin mitigates DSS-induced colitis by targeting senescence and inflammation and restoring beneficial bacteria in the gut | Ashiqueali et al. (2024) |
| | Pre-clinical animal model- progeroid mice and wild-type old mice and *in vitro* human adipose tissue | -↓senescence markers ($p16^{Ink4a}$ and p21 and SASP factors<br>-↑lifespan, ↓ age-related pathology and restored tissue homeostasis in wild-type old mice | | | Yousefzadeh al. (2018) |
| | Clinical trial phase II + 70 y.o adults (recruiting) | -Blood markers of inflammation and frailty | | Ongoing study | ClinicalTrials.gov ID NCT03675724 |
| **Oleuropein** | Pre-clinical *in vitro* model- fetal lung fibroblasts in a pre-senescent state | -↓levels of IL−8 and VEGF (SASP factors) in senescent fibroblast-conditioned medium collected after oleuropein treatment | | Oleuropein can modulate angiogenesis indirectly by acting on local senescent fibroblasts | Margheri et al. (2019) |
| | Pre-clinical animal model- induced colitis rat model | | -↓ levels of proinflammatory cytokines in colonic tissues (IL1β, TNFα, IL10, COX−2, iNOS, TGFβ1, MCP−1, and NF-κB)<br>-↓mortality rate and disease activity index | Oleuropein had intestinal anti-inflammatory, antioxidant, and anti-apoptotic effects in an ulcerative colitis experimental model | Motawea et al. (2020) |
| **Quercetin** | Pre-clinical animal model | -↓SA-β-Gal and ↓p16 and p21 gene expression in adipose tissue; no results in liver and muscle tissues | | D+Q attenuates adipose tissue inflammation and improves systemic metabolic function in old age | Islam et al. (2023) |
| | Phase I clinical trial- open label pilot study for patients with idiopathic pulmonary fibrosis | -↓SA-β-Gal and ↓p16 and p21 in adipose tissue cells<br>-↓Skin epidermal $p16^{INK4a+}$ and $p21^{CIP1+}$ cells and SASP factors, including IL1α, IL6 | | | Hickson al. (2019) |
| | Pre-clinical animal model- colitis induced mice | | -↓production of pro-inflammatory cytokines, such as interleukin IL17, TNFα, and IL6<br>-↑Bacteroides, *Bifidobacterium*, *Lactobacillus*, and *Clostridia* | Dietary quercetin exerts therapeutic effects on induced colitis, probably due to its ability to suppress pro-inflammatory cytokines and/or modify gut microbiota | Lin et al. (2019) |
| **Resveratrol** | Pre-clinical animal model- colitis induced mice | | -↓colonic tissue damage;<br>-↓expression of the pro-inflammatory cytokines IL1β, IL6, KC/GRO, and TNFα;<br>-↑ abundance of *Bifidobacterium*; | Dietary resveratrol attenuated inflammatory status and alleviated gut microbiota dysbiosis in a colitis mouse model | Li et al. (2020) |
| | Clinical trial phase II- randomized, double-blind, placebo-controlled pilot study | -↓plasma levels of TNFα<br>-↓activity of NFκB in peripheral blood mononuclear cells | | Resveratrol supplementation can reduce inflammation in UC patients | Samsami-Kor et al. (2015) |
| **Taxifolin** | Pre-clinical animal model- colitis induced mice | | -↓TNFα, IL1β, and IL6 in colonic tissue<br>-↑levels of butyric acid and isobutyric acid in the feces;<br>↑*Akkermansia* and *Lactobacillus* | Taxifolin can alleviate DSS-induced colitis by altering gut microbiota to increase the production of SCFAs | Li et al. (2022) |
| | Pre-clinical animal model- D-gal-based aging mouse model | -↓ROS levels<br>-↑nuclear factor-erythroid 2-related factor 2 (Nrf2)<br>-↑Abundance of *Enterorhabdus*, *Clostridium*, *Bifidobacterium*, and *Parvibacter*<br>-Restored spatial learning and memory<br>-Alleviated histopathological and structural damage of mouse brain tissue | | Taxifolin alleviated oxidative stress injury and regulated intestinal microbes in aged mice and improved the overall aging process | Liu et al. (2021) |

(*continued on next page*)

**Table 1** (*continued*)

| Compound | Type of study | Senescence pathways targeted | Gut-related effects | Main outcomes | References |
|---|---|---|---|---|---|
| **Carnosic acid** | Pre-clinical animal model- colitis induced mice | | -Restored bacterial diversity<br>-↑abundance of *Bifidobacterium*<br>-↑abundance of *Lactobacillus*<br>-Microbiota-derived metabolites positively correlated with anti-inflammatory effects | Oral administration of carnosic acid attenuated DSS-induced colitis in mice | Zhang et al. (2023) |
| | Pre-clinical animal model- D-gal-based aging mouse model | -↓expression of p53, p21 and p16;<br>-↓SA-β-Gal activity<br>-↓levels of IL6 and TNFα | | Carnosic acid protects against premature senescence induced by oxidative stress and D-gal, related to the antioxidative, anti-inflammatory roles of carnosic acid and inhibition of non-enzymatic glycosylation | Su et al. (2020) |
| **Ginsenosides** | Pre-clinical animal model: dysbiotic mice | | -↑Bacteroides, *Alloprevotella* and *Blautia*<br>-Restored gut microbiota diversity<br>-↑SCFA levels<br>-↑expression of tight junction proteins<br>-↓ TNFα, IL1β, and IL6 | Rk3 reduces intestinal inflammation and induces potentially beneficial changes in the gut microbiota | Bai et al. (2021) |
| | Pre-clinical *in vitro* model: Human Dermal Fibroblasts | -↓p16, p21, and p-p53 expression levels in old HDFs treated with Rg3<br>-↓SA-β-Gal activity | | Ginsenoside Rg3 partially reversed senescence of HDFs through induction of antioxidant enzymes | Jang et al. (2020) |
| **Fucoxanthin** | Pre-clinical model: high fat-fed mouse model | | -↑*Lactobacillus/ Lactococcus*, *Bifidobacterium*, and some butyrate-producing bacteria<br>-↓*Lachnospiraceae* and *Erysipelotrichaceae*<br>-↓IL6 and TNFα<br>-↑IL10<br>-Increased microbiota diversity | Fucoxanthin has the potential to alleviate the development of obesity and related symptoms through mediating the composition of gut microbiota | Sun et al. (2020) |
| | Pre-clinical animal model- colitis induced mice | | -↑*Firmicutes* to *Bacteroidota* (F/B) ratio<br>-↑*Lactobacillaceae* and *Lachnospiraceae*<br>-↑expression of tight junction proteins<br>-↓concentration of TNFα, IL1β, and IL6<br>-Alleviated histopathological changes in the colon | Fucoxanthin contributed to restoring the richness and diversity of gut microbiota | Yang et al. (2024) |
| | Pre-clinical animal model: age-related macular degeneration rat model | -↓SA-β-Gal activity<br>-↓ROS levels | | Fucoxanthin may protect against premature senescence and cellular dysfunction in retinal cells by oxidative stress | Chen et al. (2021) |
| | Pre-clinical *in vitro* model: human cells LECh4 | -↓SA-β-Gal activity<br>-↓superoxide accumulation<br>-↓$p18^{Ink4c}$, $p16^{Ink4a}$, and $p21^{Cip1}$ gene expression | | Fucoxanthin altered cellular processes such as ribosome biogenesis, lipid metabolism, and cell cycle regulation including some age-related pathways | Guvatova et al. (2020) |
| Geraniol | Pre-clinical animal model- colitis induced mice | | -↓levels of IL1β, IL17, IFNγ, and TNFα<br>-histological and clinical improvements in Geraniol treated-mice<br>-↑*Lactobacillaceae*, *Bacillaceae*, and *Bacteroidetes* families | | De Fazio et al. (2016) |
| | Clinical trial, Phase II: randomized, double-blinded, placebo-controlled trial | | -↓ IBS symptoms<br>-↓abundance of *Ruminococcaceae*, *Oscillospira* genera and *Erysipelotrichaceae* and *Clostridiaceae* families<br>-↑ abundance of *Faecalibacterium* | Geraniol food supplement was effective in treating overall IBS symptoms together with an improvement in gut microbiota profiles | Ricci et al. (2022) |
| | Pre-clinical animal model: hamster buccal pouch (HBP) carcinogenesis | -↓expression of COX−2 and NF-κB<br>-↓expression of VEGF (angiogenic marker)<br>↓expression of p53 and Bcl−2 | | Geraniol has potent anti-inflammatory, anti-angiogenic, anti-cell proliferative, and apoptosis-inducing properties | Vinothkumar et al. (2012) |

## Declaration of Competing Interest

The authors declare no conflict of interest.

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