



# Nutritional components as mitigators of cellular senescence in organismal aging: a comprehensive review

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**Abstract** The process of cellular senescence is rapidly emerging as a modulator of organismal aging and disease. Targeting the development and removal of senescent cells is considered a viable approach to achieving improved organismal healthspan and lifespan. Nutrition and health are intimately linked and an appropriate dietary regimen can greatly impact organismal response to stress and diseases including during aging. With a renewed focus on cellular senescence, emerging studies demonstrate that both primary and secondary nutritional elements such as carbohydrates, proteins, fatty acids, vitamins, minerals, polyphenols, and probiotics can influence multiple aspects of cellular senescence. The present review describes the recent molecular aspects of cellular senescence-mediated understanding of aging and then studies available evidence of the cellular senescence modulatory attributes of major and minor dietary elements. Underlying pathways and future research directions are deliberated to promote a nutrition-centric approach for targeting cellular senescence and thus improving human health and longevity.

**Keywords** Cellular senescence · Aging · Nutrition · Carbohydrates · Vitamins · Polyphenols · Fatty acids

## Introduction

Human health is a culmination of dynamic interactions and regulations by several genetic, non-genetic, and environmental factors. The regulatory systems of the body work intricately and coordinately to maintain functional homeostasis in cells and tissues by sensing and regulating nutrient availability and response, cell division and regeneration, thwarting off foreign and infectious agents as well as keeping memory and swiftness of the neurological responses. These systems are invariably deregulated during aging and diseases, and any preventive or therapeutic approach attempts to reinstate this ‘healthy’ state of homeostasis (van Beek et al., 2016). Aging is recognized as the single most influential risk factor that dramatically enhances the frequency and susceptibility of the elderly to several critical illnesses including the defining disorders of the twenty-first century, i.e., cancer and diabetes as well as the ongoing COVID-19 pandemic (Chen et al., 2021a; Fulop et al., 2019; Niccoli and Partridge, 2012). Organismal aging seems inevitable, and yet understanding of the underlying cause(s) and mechanisms of aging have long remained ambiguous and perplexing largely due to its stochastic and multifaceted nature. However, advances in our current molecular concepts of aging are beginning to answer some of the fundamental questions related to the evolutionary significance of aging as well as its predisposition to age-associated disorders. Unlike growth and development, aging is not considered a programmed process, (Blagosklonny, 2013), and accumulating evidence suggests that the observable macro phenotype of aging is essentially a culmination of microscopic cellular damage that builds up over time (Rattan, 2008; Yin and Chen, 2005). In fact, a strong view is now developing that understanding aging itself should be considered central for comprehending various age-related diseases and the development of

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common mitigative strategies (Blagosklonny, 2012; Hayflick, 2021; Le Bourg, 2022). In this regard, the process of cellular senescence is emerging as an over-arching phenomenon that seemingly links cellular aging to organismal aging, and therefore, a cellular senescence-centric view of aging is rapidly gaining attention (Borghesan et al., 2020; Jeyapalan and Sedivy, 2008). Perhaps even more strikingly, cellular senescence is also considered a common underlying causative factor in the pathogenesis of distinct age-related human disorders including but not limited to arthritis, diabetes, neurodegenerative disorders, sarcopenia, cancer, and cardiovascular diseases thereby enabling gerontologists to study age-related diseases through a novel and integrative approach (Borghesan et al., 2020; Kaur and Farr, 2020).

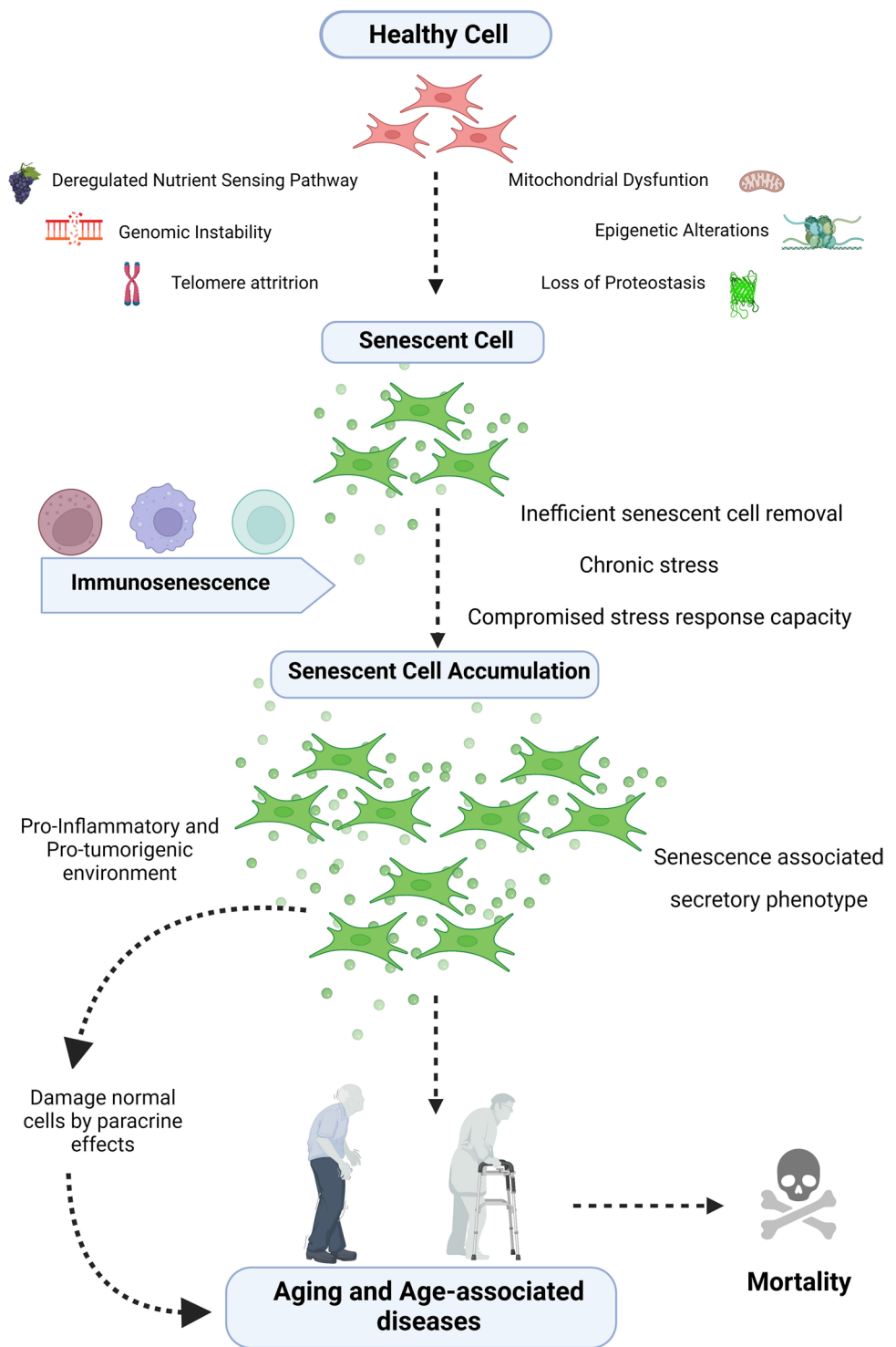
Targeting cellular senescence and its phenotype is rapidly gaining attention as a highly useful strategy in expanding organismal healthspan and lifespan (Soto-Gamez and Demaria, 2017; Yuan et al., 2020). This also paves way for developing probable anti-aging or healthy aging therapies such as the identification and development of ‘geroprotectors’ (Aliper et al., 2016). While anti-aging may seem a far-fetched and philosophically contentious phenomenon; the notion of healthy aging appears to be a valid strategy that may prevent the aggravation or frequency of chronic or fatal diseases, thereby resulting in improved healthspan and/or lifespan (Kritchevsky, 2016). Amongst the non-genetic factors, exercise, lifestyle, and nutrition are the only known modulators that can favorably influence health and aging. Further, nutrition is considered the single most potent factor that can mitigate some of the deleterious aspects of aging including predisposition to diseases, and thus a novel discipline called ‘nutrigerontology’ has recently been emphasized (Verburgh, 2015). The present narrative review delineates the current cellular senescence-centric molecular understanding of aging and its interdependent effects on the fundamental regulatory systems of the body. We then discuss the influence of primary and secondary nutritional components in modulating different aspects of cellular senescence and disease and deliberate probable research opportunities.

### Cellular senescence in aging: molecular mechanisms and systemic effects

Aging has long remained a philosophical and scientific mystery (Medawar, 1952). From a biological perspective, the aging organismal phenotype is essentially considered a time-dependent accumulation of a variety of molecular and cellular damage that hampers tissue/organ functions ultimately predisposing the elderly to morbidity and mortality (Rattan, 2008; Yin and Chen, 2005). Although several theories of aging have been put forward, an all-encompassing theory explaining the *what*, *why*, *where*, and *how* of aging

has remained elusive. Notwithstanding this, accumulating studies are now beginning to uncover some of the fundamental aspects of aging, and in the process have also highlighted the intricacies of the process. In particular, the role of cellular senescence as the causal nexus explaining various facets of aging is gaining attention amongst gerontologists (Borghesan et al., 2020). Cellular senescence was first identified in fibroblasts by Hayflick and Moorhead back in 1961; (Hayflick and Moorhead, 1961), however, it was initially perceived as an *in vitro* artifact, and its acceptance as a mainstream aging theory was dismissed for a long time (Cristofalo et al., 2004). Observations in the last decade have now shown conclusive evidence that cellular senescence is indeed a ‘hallmark of aging’ which may potentially serve as a connecting factor among other known hallmarks of aging (López-Otín et al., 2013). Cellular senescence describes a morphologically, biochemically, and metabolically distinct state wherein the cells permanently lose the capacity to divide and enter a stable cell cycle arrest. These cells are then referred to as senescent cells (SC) and are characterized by shortened telomeres, hypertrophy, altered chromatin structure, accumulation of DNA damage and reactive oxygen species (ROS), activation of cell cycle inhibitory pathways (p53, p16<sup>Ink4a</sup>, and/or p21<sup>CIP1</sup>), senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -gal) activity, resistance to apoptotic cell death, and development of senescence-associated heterochromatic foci (Fig. 1) (Campisi, 2013; Kim and Kim, 2019). In addition, SC are also accompanied by a chronic pro-inflammatory behavior known as senescence-associated secretory phenotype (SASP) which consists of increased expression of a cell-specific battery of pro-inflammatory cytokines and growth factors (Birch and Gil, 2020). Development of SC is a complex process but is invariably linked to chronic exposure to cellular stress (Ben-Porath and Weinberg, 2004). Cellular and metabolic stressors can activate either apoptosis or cellular senescence program depending upon the type and duration of the stressor. Although the exact dichotomy of this cellular fate under stress is still debatable, (Childs et al., 2014) it is accepted that chronic stress conditions can propel the cells towards a senescence program. During the course of organismal lifespan, cells are threatened by various internal and external stressors, and indeed, a link between dysregulated organismal stress response capacity and the development of SC has been observed (Zhang et al., 2017). Inherent deficiencies in the replication of telomeric regions of the chromosomes with each cell division result in ‘replicative senescence’ (Campisi, 1997) while premature senescence can also be induced in cells through acute or chronic stress exposure (stress-induced premature senescence) (Toussaint et al., 2000; Toussaint et al., 2002). Further, cellular senescence is no longer considered a phenomenon related only to somatic proliferative cells, as terminally differentiated cells such

**Fig. 1** Schematic representation of development of senescent cells and their deleterious effects with age. Chronic intrinsic and extrinsic stressors augment cellular and macromolecular damage resulting in deregulation of cell signalling and activation of cellular senescence pathways. The age-related impairment of the immune system contributes to the inefficient systemic clearance of senescent cells thereby aiding in increased senescent cell burden in tissues. The SASP of accumulating senescent cells promotes pro-inflammatory and pro-tumorigenic environment thereby predisposing elderly to increased morbidity and mortality

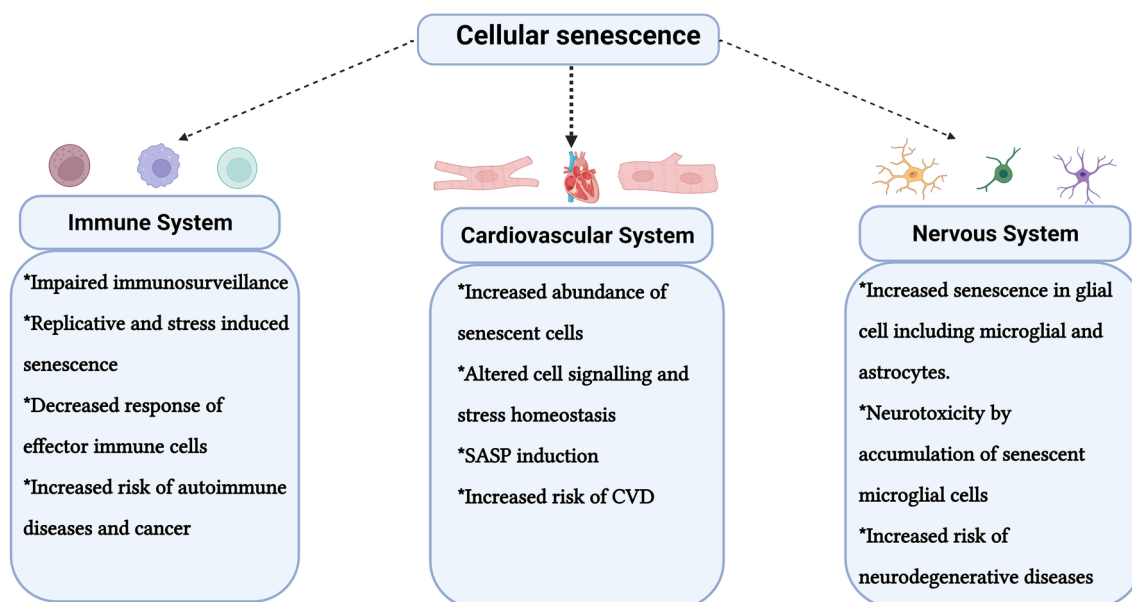


as immune cells or adipocytes are also known to undergo senescence (von Zglinicki et al., 2021). It is pertinent to note that SC are not necessarily undesirable by themselves as these cells are important mediators of certain physiological processes such as wound healing (Demaria et al., 2014) and even embryonic development (Muñoz-Espín et al., 2013). However, it is the age-associated gradual accumulation of

SC in various tissues and organs which has been correlated with an increased risk of disease and death (Fig. 1) (Idda et al., 2020; Krishnamurthy et al., 2004; Yousefzadeh et al., 2020). Indeed, studies have shown that targeted removal of SC through agents called ‘senolytics’ can enhance the lifespan, alleviate systemic inflammation, improve organ functions, and also mitigate characteristic age-related disorders

such as diabetes (Aguayo-Mazzucato et al., 2019; Baker et al., 2011; Baker et al., 2016; Xu et al., 2018). Conversely, the addition of SC to healthy tissues can induce premature aging and disease-like phenotype suggesting that SC are sufficient to drive age-related pathologies (Kim et al., 2020; Xu et al., 2016). As SC accumulate in tissues and organs, the chronic presence of SASP becomes increasingly detrimental as it affects nearby healthier cells through paracrine effects resulting in pro-inflammatory and pro-tumorigenic environment (Birch and Gil, 2020). There is also evidence that the rate of development of SC is not linear with age and is also tissue-dependent suggesting variable predisposition to biological aging depending upon the tissue type (Karin et al., 2019). We have also recently reported that adipose tissue is more vulnerable to the development of age-associated senescence-like features which were predominant from the age of 14 months in experimental mice (Sharma et al., 2022). A startling common link between SC and various age-related diseases is also rapidly gaining attention. There is evidence that SC accumulation might play a direct role in the pathogenesis and/or exacerbation of disorders such as type I and type II diabetes (Aguayo-Mazzucato et al., 2019; Thompson et al., 2019), osteoarthritis (Xu et al., 2016), cognitive functional decline (Lye et al., 2019), as well as cancer (Liu and Hornsby, 2007). It is conceivable that age-related disorders may be linked to the basic process of aging, and thus strategies aimed at targeting these disorders within the purview of cellular senescence and aging may provide a new therapeutic as well as economic perspective to the traditional disease-specific research focus (Blagosklonny, 2018; Boccardi and Mecocci, 2021; Scott et al., 2021).

The systemic effects of cellular senescence on key regulatory bodily systems and their related disorders are increasingly being deciphered (Fig. 2). The immune system is gaining central attention in this regard and a bidirectional relationship between cellular senescence and the immune system is rapidly emerging (Sharma, 2021). The immune system is considered to play a critical role in regulating the accumulation of SC in tissues and it is speculated that loss of immune functions with age could impair systemic SC clearance and therefore increase SC burden (Kale et al., 2020; Sharma, 2021). This is because SC are immunogenic and are recognized and removed by cells of the immune system such as NK cells in young healthier organisms (Kale et al., 2020). The chemotactic factors in the SASP of young organisms attract immune cells to the location of accumulating SC which ultimately results in their removal. However, as we age, the gradual restructuring of the immune system through the process of immunosenescence appears to deter their immunosurveillance and phagocytic potential which may contribute to hampered identification and removal of SC. For example, it was demonstrated that in vivo deficiency in cytotoxic response of effector immune cells can enhance the accumulation of SC in tissues accompanied with chronic inflammation (Ovadya et al., 2018). Further, a recent study observed that DNA damage and senescence in murine hematopoietic cells are sufficient to drive systemic effects of cellular senescence thereby implying the critical role of the immune system in driving organismal aging (Yousefzadeh et al., 2021). It is thus not surprising that senescent immunotherapy is considered a promising anti-aging strategy (Burton and Stolzing, 2018). On the other hand, similar to



**Fig. 2** Effects of cellular senescence on major regulatory systems of body during aging

other cells, immune cells are also liable to undergo cellular senescence, and thus, together with immunosenescence, immune cells are significantly impacted with age although this dichotomy remains to be completely resolved (Sharma, 2021). Another dimension to this intricate association was revealed when it was observed that SC can actively develop strategies to evade their immune system-mediated clearance similar to cancer cells (Pereira et al., 2019). Thus, the immune system and cellular senescence are interlinked, and exploring their interrelationships and biological effects is an active area of research. In addition to the immune system, cells of the cardiovascular system such as cardiomyocytes and endothelial cells have been shown to present characteristic features of age-associated cellular senescence that have been implicated in the development of age-related cardiovascular disorders (CVD) (Fig. 2). Although the molecular mechanisms governing CVD are largely unknown, accumulating evidence suggests a key role of cellular senescence in the pathogenesis of CVD (Shakeri et al., 2018), and targeting SC has been argued as a potential therapeutic opportunity against various deleterious aspects of CVD (Childs et al., 2018). For instance, in response to toxic agents, cardiomyocytes exhibit increased ROS levels and persistent DNA damage that upregulates characteristic senescence markers such as p16<sup>INK4a</sup>, p21<sup>CIP1</sup>, and SA- $\beta$ -gal expression (Mitry et al., 2020). It was recently demonstrated that human and murine cardiomyocytes acquire a senescent-like phenotype characterized by overexpression of p21<sup>CIP1</sup> and p16<sup>INK4a</sup> resulting in the development of pro-fibrotic and pro-hypertrophic environments and thus contributing to age-related myocardial dysfunction (Anderson et al., 2019). Crucially, pharmacological clearance of SC in mice alleviated some of the deleterious aspects of cardiac aging, including myocardial hypertrophy and fibrosis (Walaszczyk et al., 2019). Vascular endothelial cell senescence is also emerging as a prominent contributor to CVD as it may affect vascular permeability, repair, and angiogenesis (Jia et al., 2019). Aged endothelial cells show characteristics of SC such as reduced telomere length, increased DNA damage foci formation, SASP induction, and elevated intracellular ROS production (Hohensinner et al., 2016; Khan et al., 2017). A recent report has shown that EC senescence is not only detrimental to CVD but can also induce metabolic disorders by impairing insulin sensitivity through the senescence-associated secretory phenotype (Barinda et al., 2020). Similar to cardiovascular disorders, cellular senescence is also considered a key player in regulating age-dependent neurodegenerative diseases (Fig. 2) (Si et al., 2021). For example, senescent astrocytes accumulate in Alzheimer's patients wherein they promote inflammation through the SASP (Bhat et al., 2012; Walker et al., 2020) while attenuation of cellular senescence has been shown to alleviate neuroinflammation associated with Alzheimer's (Hou et al., 2021). In addition, a recent

study revealed that senescent neurons with tau neuropathology are also prevalent in patients with AD (Dehkordi et al., 2021) while removal of accumulated senescent glial cells attenuated cognitive decline and age-related neurodegenerative disorders (Bussian et al., 2018). Explicatively senescent glial cells have been observed during aging which contribute to the pathology of AD (Hu et al., 2021). During aging, brain microglia show characteristic expression of senescence markers such as telomere shortening, SA- $\beta$ -gal activity, altered metabolic profile, and increased oxidative stress (Greenwood and Brown, 2021). In-state of senescence, microglia are neurotoxic and become detrimental in many neurodegenerative diseases by producing inflammation, inflammatory cytokines, superoxide anions, and nitric oxide (Nakajima and Kohsaka, 2004; Streit, 2002). Taken together, these observations suggest that cellular senescence is an important determinant in regulating the functional efficacy of major regulatory systems of the body with age and thus is a promising therapeutic target.

## Primary diet constituents and cellular senescence

### Carbohydrates

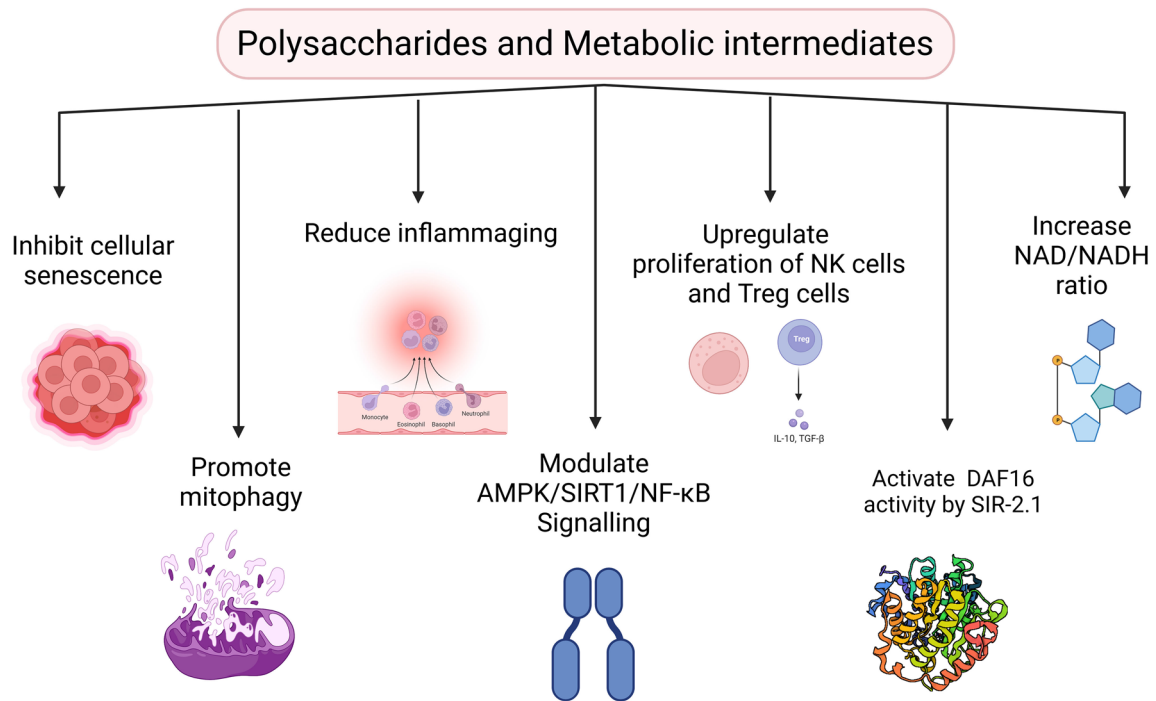
Carbohydrates are primary sources of cellular energy although their role in cell structure and signaling is also known. Carbohydrate metabolism is of great significance during aging as an association between carbohydrate consumption and chronic disorders such as obesity and diabetes is well recognized (Kelly et al., 2020). Besides, diets rich in glucose and fructose have been shown to accelerate aging in model organisms while a reduction in carbohydrate intake is often associated with reduced severity of disorders such as diabetes (Feinman et al., 2015). However, low carbohydrate diets and their significance during aging are still controversial and contradictory (Mooradian, 2020). Regardless, it is crucial to consider that complex carbohydrates and/or their derivatives have been demonstrated to suppress cellular senescence and augment healthy aging. For instance, a recent study showed that a heteropolysaccharide derived from the medicinal herb *Astragalus membranaceus* alleviated hepatocyte senescence by inhibiting the development of cellular senescence and promoting mitophagy via mTOR pathway both in vitro and in vivo (Yao et al., 2021). Another recent report demonstrated that *Astragalus* polysaccharides can reduce glucose-induced premature senescence and inflammasome activation in rat aortic endothelial cells (Miao et al., 2022). Using a d-galactose induced aging mice model, the application of *Aronia melanocarpa* heteropolysaccharides successfully ameliorated inflammation and aging in mice by modulating the AMPK/SIRT1/NF- $\kappa$ B signaling pathway and gut microbiota (Zhao et al., 2021).

Studies on polysaccharides isolated from the herb *Angelica sinensis* have revealed anti-cellular senescence and antioxidant attributes in haematopoietic cells and endothelial progenitor cells while in vivo suppression of cellular senescence and improvement in brain senescence in a murine model of d-galactose induced aging was also observed (Cheng et al., 2019; Lai and Liu, 2015; Mu et al., 2017; Xiao et al., 2017). Similarly, the polysaccharide TLH-3 isolated from the mushroom *Tricholoma lobayense* alleviated premature cellular senescence in vitro and improved in vivo markers of senescence and SASP in premature aging mice (Pan et al., 2018). Also, polysaccharides extracted from the medicinal plant *Lycium barbarum* prevented the augmentation of oxidative stress-induced epithelial senescence and apoptosis in human lens epithelial cells in vitro (Qi et al., 2014). Another report revealed that marine sulphated polysaccharide Fucoidan can rescue endothelial cells from cellular senescence, and improve their survival, proliferation, and functional response which was implicated in enhanced neovasculogenic potential in vivo (Lee et al., 2015). Daily administration of polysaccharides isolated from Korean ginseng berry to old C57BL/6J mice resulted in improved indices of immunosenescence and inflamm-aging characterized by increased proliferation of Treg and NK cells, reduced systemic inflammatory molecules, and attenuation of thymic involution (Kim et al., 2018). Previous studies have also identified the role of metabolic carbohydrate intermediates in extending lifespan in model organisms by modulating nutrient signalling pathways. For instance, *Caenorhabditis elegans* (*C. elegans*) when treated with trehalose extends lifespan by lowering insulin/insulin growth factor-1 signaling and suppressed aging by offsetting stressors (Honda et al., 2010). In aged *Saccharomyces cerevisiae* cells, trehalose accumulation elicited an anti-aging response and increased ethanol production (Trevisol et al., 2011). Another study demonstrated the role of pyruvate in extending the lifespan of *C. elegans* by improved tolerance to oxidative stress via amplified mitochondrial pyruvate metabolism (Mouchiroud et al., 2011). Tricarboxylic acid cycle metabolites like malate and fumarate are also linked with lifespan extension in *C. elegans* via regulation of transcription factor DAF-16/FOXO, histone deacetylase SIR-2.1 and increasing the amount of oxidized NAD and FAD cofactors (Edwards et al., 2013; Sun et al., 2017). Oligosaccharides like *N*-glycan and *N*-acetylglucosamine supplementation reduced aggregation of proteins via ER-associated protein degradation, proteasomal activity, and autophagy consequently extending lifespan in *C. elegans* (Denzel et al., 2014). In a pre-clinical study, chitosan oligosaccharides have been utilized as a therapeutic agent against age-related illnesses (Kong et al., 2018). Together, these findings suggest that complex carbohydrates and intermediates of carbohydrate metabolism can regulate aging by modulating cellular senescence, proteostasis,

and inflammation. However, adequate carbohydrate intake must be monitored since a high carbohydrate diet is associated with an increased risk of mortality in clinical studies (Dehghan et al., 2017). Together, it is reasonable to assert that although carbohydrates are often neglected concerning their bioactivity, especially with regard to aging, a carefully curated carbohydrate-rich diet could be potentially useful in mitigating cellular senescence which should be explored further (Fig. 3).

### Dietary proteins and amino acids

Proteins and amino acids are major structural and functional constituents of cells. In addition to carbohydrates, proteins are an essential part of the human diet and attempts have been made to ascertain a suitable carbohydrate to protein ratio in diets for augmenting health and aging. In this regard, a low protein (< 10% of calories from protein) and high carbohydrate diet, often in the ratio of 1:10, has scientific evidence of improving health during aging and extending the lifespan (Le Couteur et al., 2016; Levine et al., 2014). It was observed that even a short-term low protein and high carbohydrate diet regimen in mice can improve indices of metabolic health indicated by levels of insulin, glucose, lipids, and homeostatic model assessment (HOMA), and surprisingly these effects were similar to the stricter calorie restriction diet despite an increase in total energy intake (Solon-Biet et al., 2015). On the other hand, consumption of a high protein diet (> 20% of calories from protein) amongst the elderly augmented all-cause mortality incidences by 75% and increased the risk of cancers by 400% suggesting the detrimental effects of high protein consumption during aging (Levine et al., 2014). In addition, impaired protein metabolism appears to be intimately linked to cellular senescence and organismal longevity. A recent study compared the proteomic profile of fibroblast cells across species and reported that long-lived animals tend to have lower turnover rates of highly abundant cellular proteins which eventually results in lower oxidative stress and efficient energy management (Swovick et al., 2021). Further, restriction of protein synthesis suppressed cellular senescence both at the cellular and organismal levels (Takauji et al., 2016). Moreover, the balance between cellular protein synthesis, folding, and degradation (proteostasis) is also impaired in SC, and maintenance of proteostasis is considered a key therapeutic mechanism regulating senescence (Joy et al., 2021; Sabath et al., 2020). These observations augment the rationale that protein consumption, cellular metabolism, and energy homeostasis are intimately linked which can affect organismal longevity. However, studies examining the impact of dietary proteins and specific amino acids on cellular and organismal senescence are limited. A recent study observed that consumption of protein-rich diets can accelerate tissue



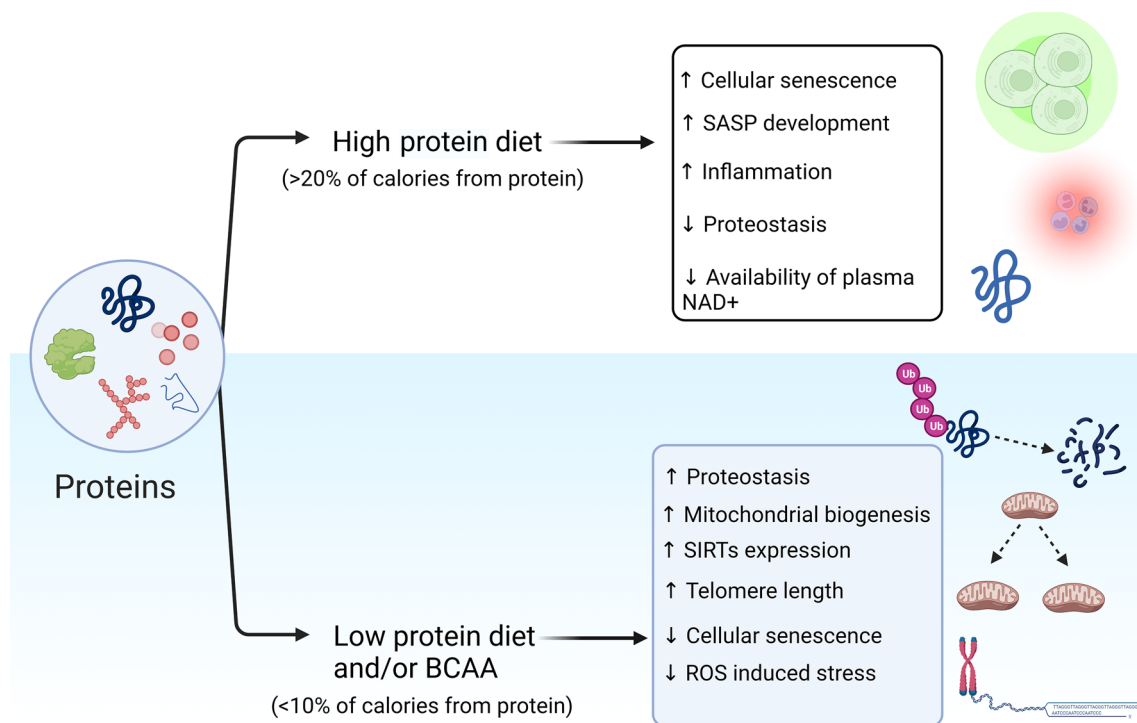
**Fig. 3** Modulation of cellular senescence by dietary polysaccharides and metabolic intermediates of carbohydrate metabolism

senescence and SASP development in mice and thus promote the deleterious effects of aging (Nehme et al., 2021). Another study observed that protein-rich diets are associated with reduced availability of plasma NAD<sup>+</sup> levels and inflammation in healthy middle-aged adults indicating that protein-deficient diets might promote longevity by improving cellular energy expenditure and expression of enzymes such as SIRT1s (Seyedsadjadi et al., 2018). In terms of specific amino acids, it has been observed that amino acids can both promote and limit organismal lifespan and senescence, and thus amino acids can be used as markers of longevity (Rallis et al., 2020). In particular, the metabolism of branched-chain amino acids (BCAA) is associated with the regulation of human aging (Mansfeld et al., 2015). It was previously reported that supplementation of BCAA can improve mitochondrial biogenesis, alleviate ROS-induced stress, and thus augment lifespan in aging mice (D'Antona et al., 2010). In terms of cellular senescence, it was reported that cellular supplementation with BCAA can augment senescence-induced tumor suppression in liver cancer cells (Nakano et al., 2013) while a recent study has observed that higher circulatory levels of BCAA are positively associated with longer telomere lengths and thus suppressed systemic cellular senescence in middle-aged subjects (Fig. 4) (Zhang et al., 2020). In addition to the quantity of proteins consumed, the source of proteins (animals or plants) in diet also appears to strongly impact organismal lifespan although deeper studies relating these aspects to cellular senescence are warranted

(Song et al., 2016). Further, information on SASP modulatory and senolytic attributes of proteins and dietary amino acids is rare and needs further exploration.

### Fatty acids

Fatty acids are essential structural and signaling molecules in cells. Essential fatty acids must be supplied in the diet and their critical role in maintaining growth and including aging is well recognized (Lai et al., 2018). In particular, omega-3-polyunsaturated fatty acids (PUFA) have shown several beneficial effects in ameliorating age-related insults including inflammation, osteopenia, type II diabetes, and imparting vasodilatory properties (Cugno et al., 2021; Simopoulos, 1999). In fact, a recent study has demonstrated that higher circulating levels of marine n-3 PUFA are associated with a lower risk of premature death (Harris et al., 2021). In addition, immunomodulatory and anti-immunosenescence activities of omega-3-fatty acids rich fish oil have also been reported. For instance, the consumption of fish oil can accelerate the phagocytic activity of immune cells, increase CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes, reduce inflammatory cytokines, and can increase muscle strength in the elderly (de Lourdes Nahhas Rodacki et al., 2015, Rodacki et al., 2012). Supplementation of fish oil ameliorated rosiglitazone-induced osteopenia in aging C57BL/6 mice resulting in a higher bone density, reduced pro-inflammatory cytokines, and increased anti-inflammatory cytokines in aging mice (Cugno et al.,



**Fig. 4** Influence of dietary protein intake and specific amino acids on different aspects of cellular senescence

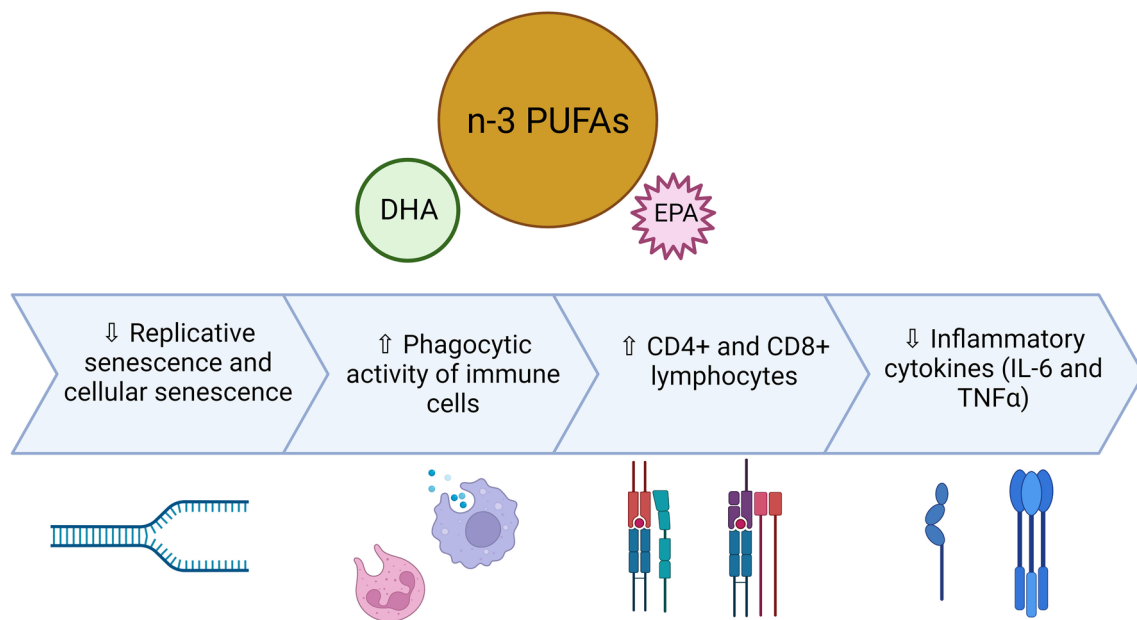
2021). Furthermore, research proposes that supplementation of eicosapentaenoic acid may decrease NK cell activity in older individuals (Thies et al., 2001). Fish oil rich in omega-3 fatty acids attenuated various cardiac dysfunctions from ventricular hypertrophy to cardiac remodeling, as seen in aging mice (Halade et al., 2011). In addition, a central role of lipids in regulating both replicative and stress-induced cellular senescence is also rapidly emerging (Millner and Atilla-Gokcumen, 2020). In general, SC display characteristics increase in cellular lipid accumulation indicating deregulated lipid metabolism (Flor et al., 2017). Further research has revealed that lipid composition undergoes global changes in SC resulting in the remodeling of cell membranes which is particularly implicated in the development of SASP (Lizardo et al., 2017). Another recent study has indicated an essential role of fatty acid synthase in the development and initiation of the senescence program in mouse hepatic stellate cells and human primary fibroblasts (Fafián-Labora et al., 2019). It is therefore not surprising that the application of fatty acids has shown promise in suppressing cellular senescence as well as improving the aging immune responses. For example, a recent clinical trial has documented that consumption of marine n-3 PUFAs in subjects with renal transplantation reduces the risk of cellular senescence and SASP damage thereby resulting in improved recovery (Chan et al., 2021). Consumption of omega-3-fatty acids has been associated with decreased replicative senescence in human immune cells by preserving their

telomere length (Farzaneh-Far et al., 2010; Kiecolt-Glaser et al., 2013). Supplementation of omega-3-fatty acids for 4 months in middle-aged subjects resulted in maintenance of telomerase activity while attenuating markers of stress and inflammation (Madison et al., 2021). Consumption of n-3 PUFA by d-galactose-induced aging mice reduced cellular DNA damage and protected the liver and testes of animals against telomere shortening (Chen et al., 2017). In a study on pigs, it was observed that supplementation with linseed oil for 9 weeks counteracted the age-related increase in the expression of TRF-1 which could be implicated in telomere length-promoting effects of PUFAs (Ogłuszka et al., 2020). Using in vitro model of stress-induced senescence in vascular endothelial cells, it was observed that supplementation with EPA and DHA can attenuate cellular senescence and its biomarkers by primarily inhibiting DNA damage and augmentation of cellular antioxidant potential (Sakai et al., 2017). Together, these observations assert that fatty acids are key mediators of the development of SC which also signifies their therapeutic potential (Fig. 5).

### Vitamins and minerals

An important role of certain vitamins in regulating cellular senescence is also emerging. In particular, vitamin D appears to influence several facets of cellular senescence both in vitro and in vivo. A recent study suggests that vitamin D deficiency and cellular senescence are related which together





**Fig. 5** Cellular senescence and immunosenescence modulatory attributes of omega-3-fatty acids during aging

influence the pathogenesis of obesity in experimental animals (Bima et al., 2021). Another recent study observed that vitamin D supplementation could rescue against doxorubicin-induced cellular senescence in human endothelial cells by upregulation of IL-10 and FOXO3a expression mediated by the modulation of pAMPK $\alpha$ /SIRT1/FOXO3a complex activity (Chen et al., 2021b). These observations are largely attributed to the ability of vitamin D to regulate cell cycle and proliferation as also reported previously (Samuel and Sitrin, 2008). Moreover, relatively higher vitamin D levels are also linked to increased telomere length and thus suppression of senescence. For instance, it was reported that subjects with higher levels of 25-hydroxyvitamin D exhibited significantly higher telomere length in whole blood cells (Mazidi et al., 2017). Similarly, two independent studies on elderly subjects also reported that serum 25-Hydroxyvitamin D is positively associated with mean telomere length suggesting that levels of 25-Hydroxyvitamin D could be predictors of telomere length and longevity (Beilfuss et al., 2017; Richards et al., 2007). Another recent study suggests that higher levels of vitamin D are positively related to longer telomere length but negatively associated with indications of type II diabetes as monitored through levels of Hb1Ac suggesting a deeper correlation between vitamin D, and cellular senescence, and age-related diseases (Akash et al., 2021). In addition to vitamin D, vitamin E is also reported to have anti-cellular senescence attributes which could be attributed to its strong antioxidant activity. For example, it was observed that treatment with vitamin E could suppress the progression of cellular senescence in human endothelial and fibroblast cells through the inhibition of cell cycle inhibitors

(La Fata et al., 2015). Moreover, inadequate consumption of vitamin E was associated with shorter telomere lengths in leucocytes of humans suggesting that appropriate dietary consumption of vitamin E can mitigate cellular senescence (Corina et al., 2019). In addition, a recent study has identified vitamin B2 as a suppressor of senescence by promoting mitochondrial energetic homeostasis indicating that dietary riboflavin could also impact aging (Nagano et al., 2021). In addition to vitamins, certain minerals also appear to be associated with cellular senescence. The mineral magnesium is reportedly active in modulating cellular senescence and aging. Chronic magnesium deficiency in cultured fibroblasts results in an accelerated senescence program characterized by increased expression of cell cycle inhibitors and SA- $\beta$ -gal activity as well as reduced telomere length (Killilea and Ames, 2008). Conversely, dietary supplementation of magnesium enhanced the mitochondrial functions and prevented oxidative stress in tissues resulting in enhanced murine lifespan (Villa-Bellosta, 2020). However, there are inconsistent reports on magnesium levels and telomere length in leucocytes which warrant further exploration (O'Callaghan et al., 2014; Yu et al., 2020). Zinc is another important mineral that is actively involved in regulating aging through modulation of the immune system (Haase and Rink, 2009) as well as through general suppression of systemic cellular stress (Giacconi et al., 2018). Zinc metabolism is impaired in SC and evidence suggests that zinc deficiency can contribute to the accumulation of SC and vascular pathology (Malavolta et al., 2017). Further, impaired zinc metabolism is also linked to shortened telomeres and increased inflammation in PBMCs (Cipriano et al., 2009) while accumulation of zinc is

associated with increased ROS production and senescence induction in vascular smooth muscle cells (Salazar et al., 2017). Iron is another important mineral that has been implicated in driving aging. In particular, blocking iron availability through chelation is considered an important lifespan-extending mechanism of several dietary natural molecules such as EGCG, berberine, and curcumin (Mangan, 2021). This is because although iron deficiency anemia is often observed in the elderly, iron stores in tissues gradually increase with age which is implicated in the inhibition of ferroptosis and thus augmentation of age-related pathologies (Mazhar et al., 2021). Further, it has been observed that iron rapidly accumulates in SC causing inhibition of iron-induced cell death and thus aiding in the survival of SC (Killilea et al., 2004; Masaldan et al., 2018). In fact, augmentation of ferroptosis and iron metabolism is emerging as a novel therapy for removing the accumulation of SC in vivo which should be further explored (Go et al., 2021).

## Secondary diet constituents and cellular senescence

### Polyphenols

Plant polyphenols are a diverse group of phytochemicals that are considered important constituents of a healthy diet due to their well-documented role in modulating human health. Polyphenols have been reported to confer cytoprotective and health beneficial effects through the modulation of several cell signaling pathways such as NRF2, NF- $\kappa$ B, mTOR, Sirtuins as well as key processes such as autophagy, immunomodulation, cell proliferation, and apoptosis (Cory et al., 2018; Vauzour et al., 2010). In addition, studies suggest that long term consumption of dietary polyphenols confers a protective role in abating a multitude of age-related degenerative diseases like cancer (Lee and Lee, 2006), cardiovascular diseases (Khurana et al., 2013), muscular atrophy (Nikawa et al., 2021), neurodegenerative diseases (Rossi et al., 2008), arthritis (Behl et al., 2021), and even organismal longevity (Queen and Tollefsbol, 2010). Current research in this domain is now focused on understanding whether and how polyphenols can modulate cellular senescence and SASP thereby impacting organismal aging (Sharma and Padwad, 2020). We and others have previously observed anti-cellular senescence attributes of isolated dietary polyphenols such as green tea EGCG (Kumar et al., 2019; Kumar et al., 2020a), berberine (Dang et al., 2020), resveratrol (Giovannelli et al., 2011), quercetin (Sohn et al., 2018), kaempferol (Yao et al., 2019), tocotrienol (Khee et al., 2014), genistein (Wu et al., 2021), pterostilbene (Jiang et al., 2021), and apigenin (Li et al., 2021) in various in vitro and in vivo settings (Table 1). Further, anti-SASP effects of dietary flavonoids apigenin and

kaempferol in bleomycin-induced senescence in fibroblasts were also reported that involved inhibition of the NF- $\kappa$ B pathway via IRAK1/I $\kappa$ B $\alpha$  signaling (Lim et al., 2015). In addition, cellular senescence suppressive attributes of polyphenol-rich fractions isolated from fruits such as lemons (Shimizu et al., 2019), grape seed extract (Wan et al., 2021; Xu et al., 2021), as well as red wine (Botden et al., 2012) have also been documented. In addition, a growing interest amongst polyphenols is the identification of novel senolytics that may selectively induce apoptosis in SC and thus alleviate SC burden in tissues with age (Li et al., 2019; Wang et al., 2021). In fact, quercetin was the first non-synthetic molecule identified with a senolytic activity (Zhu et al., 2015) and since then the combination of dasatinib and quercetin has shown promising results in alleviating SC burden in both preclinical and clinical studies resulting in improved organ functions and lifespan (Hickson et al., 2019; Novais et al., 2021). Our lab has previously identified that tea polyphenol EGCG can also act as a senolytic and can extend murine lifespan by decreasing SC burden in multiple tissues (Kumar et al., 2019; Sharma et al., 2022). Similarly, other polyphenols such as fisetin (Zhu et al., 2017) and piperlongumine (Wang et al., 2016) as well as polyphenols-rich fractions of *Silybum marianum* flower (Woo et al., 2021) have also been reported as senolytic agents. Moreover, polyphenols are known for their immunomodulatory activities and there is evidence that polyphenol consumption can also stimulate the aging immune system and prevent inflamm-aging (Baeza et al., 2010; Sharma et al., 2017). Together, polyphenols appear to confer cytoprotective and pro-longevity attributes through the inhibition of cellular senescence and improving immune responses, and therefore novel and traditional polyphenols-rich medicinal plants should be investigated for developing a nutrition-oriented holistic anti-senescence and senescence immunotherapies (Luo et al., 2021; Sharma and Padwad, 2020). Mechanistically, dietary polyphenols have shown the ability to modulate nutrient-sensing pathways (NSP) such as the mTOR and sirtuins which are implicated in their observed anti-cellular senescence effects (Davinelli et al., 2012). The NSPs act as metabolic sensors for stress and energy which can affect downstream targets to either promote or suppress cellular growth and differentiation. As such, the coordinated activation and functioning of these pathways are necessary and their molecular targeting is recognized in anti-aging therapies including calorie restriction (Pignatti et al., 2020). In terms of cellular senescence, these pathways are even more significant since SC are inherently under redox and metabolic stress and yet being stable, their NSP profile is largely deregulated (Carroll and Korolchuk, 2018). In general, SC display increased glycolysis (James et al., 2015), overactivated mTOR signaling (Kumar et al., 2019), and suppressed Sirtuins activity (Xu et al., 2020). The mTOR pathway is of particular significance in this regard as

**Table 1** Anti-cellular senescence effects of selected polyphenols

Compound	Model	Senescence type	Observations	References
EGCG	Human articular chondrocytes-knee (NHAC-kn)	IL-1 $\beta$ -stimulated human chondrocytes	EGCG (10 $\mu$ M) resulted in downregulation of expression of IL-1, COX-2, MMP-13, and p16 <sup>ink4a</sup>	Huang et al. (2021)
Carvacrol	NIH 3T3 cell line	Acrylamide- and H <sub>2</sub> O <sub>2</sub> -induced cellular senescence	Carvacrol (100 $\mu$ M) significantly reduced SA- $\beta$ -gal activity, lipid peroxidation, and increased glutathione activity	Evazalipour et al. (2021)
Tocotrienol	Primary cultures of HDFs (Human diploid fibroblasts)	Replicative senescence	Tocotrienol-rich fraction TRF (0.5 mg/mL) resulted in modulation of senescence associated-miRNA and prevented cellular senescence	Gwee Sian Khee et al. (2014)
Pterostilbene	Mice	Ethanol-triggered hepatocyte senescence	Pterostilbene (10–20 $\mu$ M) reduced SASP, cellular communication network factor 1 (CCN1) reduction via p62-mediated selective autophagy	Yiming Jiang et al. (2021)
Genistein (GEN)	Human umbilical vein endothelial cells	H <sub>2</sub> O <sub>2</sub> -induced senescence	GEN (40 and 80 $\mu$ g/mL) downregulated the expression of p16 <sup>ink4a</sup> , p21, and TXNIP, NLRP3	Wu et al. (2021)
Dasatinib + Quercetin	C57BL/6 mice	Senescent cell-transplantation	Dasatinib + Quercetin (1 $\mu$ M + 20 $\mu$ M) selective elimination of senescent cells, reduced mortality by 65%	Xu et al. (2018)
(-)-Epicatechin	Rats	Endothelial cells isolated from aged rats	Epicatechin (1 $\mu$ M) decreased SA- $\beta$ -gal activity, NO production, and increased Sirt1 expression	Ramirez-Sanchez et al. (2018)
Apigenin	Human fibroblast strains	Stress-induced senescence	Apigenin (10 $\mu$ M) suppressed SASP phenotype and its paracrine effects	Perrott et al. (2017)
Anthocyanins rich extract of <i>Ribes meyeri</i>	Murine neural stem cells	Natural replicative senescence in isolated cells	Anthocyanins rich extract of <i>Ribes meyeri</i> (100 $\mu$ g/mL) improved proliferation response, increased telomere lengths, and decreased p16 <sup>ink4a</sup> expression	Gao et al. (2020)
Ferulic acids	Human dermal fibroblasts	UVA-induced cell senescence	Ferulic acids (10–20 $\mu$ M) increased proliferation response and antioxidant capacity	Hahn et al. (2016)
Gallic acids	Rat embryonic fibroblast	H <sub>2</sub> O <sub>2</sub> -induced senescence	Gallic acids (554.25 $\mu$ M) decreased $\beta$ -galactosidase activity, reduced inflammatory cytokines, and oxidative stress markers	Rahimifard et al. (2020)
Naringenin	Myocardial cells	H <sub>2</sub> O <sub>2</sub> -induced senescence	Naringenin (40 $\mu$ M) decreased expression of cell cycle inhibitors and arrested cells, improved redox homeostasis	Da Pozzo et al. (2017)

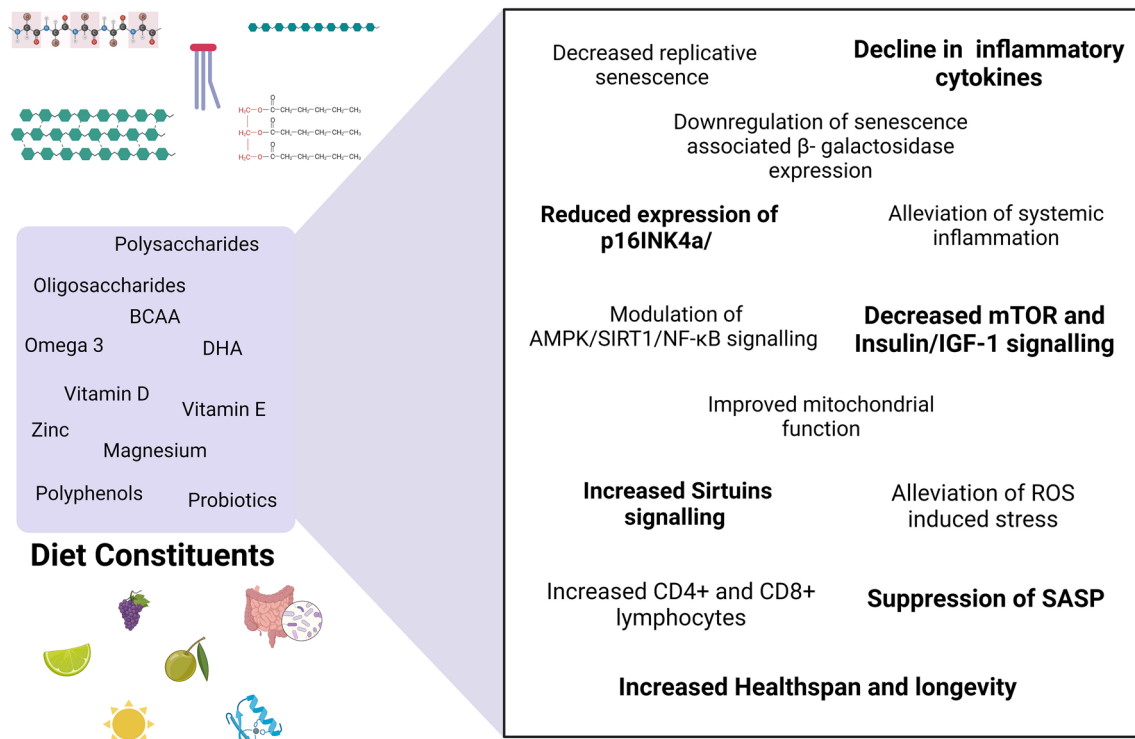
this evolutionarily conserved signaling system is considered the basal driving force of cellular senescence as it promotes the growth of non-dividing senescent cells (Blagosklonny, 2008; Liu and Sabatini, 2020). The cellular senescence modulatory effects of various dietary constituents involve interactions with these pathways to confer their cytoprotective effects. For example, we and others have observed that the anti-cellular senescence attributes of EGCG are mediated by the inhibition of mTOR pathway (Kumar et al., 2019) and activation of Sirtuins pathway (Lilja et al., 2020). Similarly, resveratrol (Demidenko and Blagosklonny, 2009) and berberine (Zhao et al., 2013) have also shown anti-cellular senescence effects mediated by the suppression of mTOR activity.

### Probiotics

It is now acknowledged that dietary consumption of probiotic bacteria can affect several facets of human health including maturation of the immune system, nutrition, and metabolism, brain development, as well as in the pathogenesis of chronic disorders such as cancer and diabetes (Cerdó et al., 2017; George Kerry et al., 2018; Maldonado Galdeano et al., 2019; Taherian et al., 2019). In fact, probiotic-derived functional foods are of attractive consumer interest and several traditional and novel probiotic fermented functional foods are available (Marco et al., 2017; Melini et al., 2019). Moreover, there is evidence that modulation of the gut microbiota could be a critical intermediate process governing the purported health beneficial effects of several dietary elements. This is primarily attributed to the fact that nutritional components first interact with the gut bacteria and their microbiota-mediated biotransformation in the gut has the potential to qualitatively and quantitatively change the physiological effects of parent molecules (Sallam et al., 2021; Wang et al., 2018). The role of gut microbiota is increasingly being emphasized in longevity and gut microbial signatures are emerging as predictors of human lifespan (Galkin et al., 2020; Wilmanski et al., 2021). Further, gut microbiota undergoes structural and compositional changes with age, dietary habits, or during disease (gut dysbiosis) and therefore supplementation with specific probiotics has been shown to improve gut dysbiosis and alleviate several deleterious aspects of organismal aging physiology such as immunosenescence (Sharma et al., 2014), neurodegeneration (Lye et al., 2018), and chronic diseases (Buford, 2017). In fact, a functional term called ‘gerobiotics’ has been recently proposed to identify new probiotics with the ability to counter aging and age-related disorders (Tsai et al., 2021). In terms of cellular senescence, it has been shown that a dysbiotic gut is a source of potential novel metabolites that can augment cellular senescence and SASP in vivo and thus augment aging and disease phenotype (Yoshimoto

et al., 2013). Conversely, we have demonstrated that secretory metabolites of probiotic *Lactobacillus fermentum* can inhibit stress-induced development of senescence and SASP in preadipocytes by improving cellular and metabolic stress (Kumar et al., 2020b). Previous studies also showed that consumption of probiotics in aged mice could prevent intestinal senescence and inflamm-aging thereby extending organismal healthspan (Jeong et al., 2015; Jeong et al., 2016). In addition, it appears that the observed anti-cellular senescence effects of dietary constituents, including phyto-molecules such as quercetin, could be mediated through the modulation of the gut microbiota composition in vivo (Saccon et al., 2021). This is an exciting new area of research as the amalgamation of probiotics and bioactive phyto-molecules such as polyphenols is considered viable and has been shown to confer cytoprotective and anti-aging effects (Banerjee and Dhar, 2019; Sharma et al., 2019).

In conclusion, cellular senescence-mediated understanding of aging and age-dependent disorders is rapidly gaining attention as a viable therapeutic target (Soto-Gamez and Demaria, 2017). It is increasingly being realized that cellular senescence could be central to developing anti-aging strategies as evidence of its integration with other established age-related phenomena such as immunosenescence and gut dysbiosis is also emerging (Budamagunta et al., 2021; Sharma, 2022). Besides, the striking presence of cellular senescence in pathophysiologically distinct human disorders renews hope of a single targetable approach to disease management during aging. Nutritional elements are essential for our survival and growth and thus their role in positively modulating cellular senescence and aging seems unsurprising. As highlighted in this manuscript, all forms of nutrition, albeit with varying degrees, have shown some potency to alleviate the different facets of cellular senescence and improve cellular functions (Fig. 6). It is exciting to note that essential nutritional components such as carbohydrates, fats, and proteins can affect the different facets of cellular senescence. However, detailed knowledge of their specific effects is still limited, and further in vivo studies are required to truly assess their anti-cellular senescence relevance. The role of minerals is also of particular interest as their impaired metabolism appears to be specific markers of cellular senescence and yet their therapeutic potential is little explored. It would be interesting to assess how specific food items rich in certain minerals could add affect the progression and development of cellular senescence. Secondary dietary elements are also of great interest as polyphenols such as quercetin have already shown promising clinical results in alleviating SC burden and improving age-related pathologies (Hickson et al., 2019). Similarly, we are only beginning to understand how probiotics can be useful in mitigating cellular senescence and aging which requires further investigations.



**Fig. 6** Potential biological effects and targets of various dietary constituents in influencing the markers of cellular senescence and related pathologies

Apart from individual components, whole diets composed of carefully curated dietary components should be assessed for their global effects on cellular senescence as also noted previously in a preliminary study (Leung et al., 2018). More such concerted efforts on different dietary regimens must be pursued for a better understanding of whole diets and their influence on cellular senescence and aging. It has long been argued that regular exercise and a healthy diet regimen is key to improving both the healthspan and lifespan. Emerging evidence now suggests that indeed both exercise and a healthy diet (e.g., Mediterranean diet) can improve the indices of general health and longevity through specific targeting of cellular senescence and its deleterious effects (Englund et al., 2021; Marin et al., 2012; Shannon et al., 2021). It is desirable that dietary constituents should be studied individually as well as in combinations of whole diets with a specific aim of identifying nutritional geroprotectors through the purview of cellular senescence that may enable a better pharmacological understanding of nutrition as a regulator of aging and diseases.

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**Declarations**

**Conflict of interest** The authors declare that they have no competing interests.

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