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Bioactive food components for managing cellular senescence in aging and disease: A critical appraisal and perspectives

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ABSTRACT

Background: A cellular senescence-centric understanding of biological aging and age-related disorders is rapidly gaining attention. As such, efforts are underway to identify geroprotectors for alleviating some of the deleterious effects of cellular senescence in aging and disease. In this regard, bioactive nutritional elements are emerging as potential candidates that can directly or indirectly influence the different aspects related to the development and progression of cellular senescence and thus impact longevity.

Methods: A detailed literature review of functional foods and dietary bioactive components including phytomolecules, probiotic bacteria, omega-3-fatty acids, vitamins, and promising healthy aging diets was conducted using the descriptors 'cellular senescence', 'aging', 'cellular stress', 'inflamm-aging', 'senolytics', 'senomorphics', 'immunotherapy', 'nutrient signaling', and 'gut microbiome' through specialized databases.

Results: Bioactive food components can suppress chronic intrinsic and extrinsic cellular stressors, selectively ablate senescent cells (SC), alleviate the inflammatory phenotype of SC, and also target cellular nutrient signaling pathways to prevent the deleterious effects of cellular senescence. In addition, integrative and novel anti-cellular senescence applications of bioactive food components mediated by interactions with the gut microbiome and modulation of the aging immune system are also emerging. Moreover, healthy diets characterized by increased carbohydrates/protein ratio have been shown to attenuate the markers of senescence and alleviate multimorbidities in clinical studies.

Conclusions: Despite limited clinical data, there is a rational basis for considering functional foods as premiere anti-cellular senescence candidates. Future research on dietary modulators of aging should be considered within the purview of cellular senescence for truly comprehending the impact of nutrition on human longevity.

1. Introduction

One of the most enduring philosophical and scientific mysteries of life is *why* and *how* we age and *whether* the age-associated deleterious effects on health can be controlled. As such, several different theories have been put forward to explain the multifaceted, heterogenous, and stochastic process of aging [1]. Today, it is generally accepted that aging is the culmination of time-dependent cellular and molecular damage that ultimately manifests as the familiar age-associated macromolecular phenotype [2,3]. However, a better understanding of the cellular and molecular pathways that drive the aging process is necessary to reduce the burden of age-associated multimorbidities and improve the lifespan. In this regard, nine different 'hallmarks of aging' were identified which together represented the common denominators of organismal aging [4]. Amongst these, the process of cellular senescence is arguably emerging as one of the most investigated and accepted explanations of biological aging and age-related diseases [5]. Cellular senescence is a physiological stress response of mammalian cells that results in the development of SC with distinct physical, molecular, and metabolic signatures [6]. SC play a direct role in the pathogenesis of age-related disorders and decreased healthspan thereof [7], while removal of SC result in improved organ functions and enhanced healthspan as well as lifespan [8,9]. Moreover, cellular senescence can better integrate with other hallmarks of aging, especially macromolecular damage and DNA damage response, thus suggesting that understanding and targeting cellular senescence is a promising approach to comprehend biological aging and its deleterious consequences [10,11].

Plant, animal, and microbial food-based nutrients are an integral part of human health which not only provide nourishment but are also critical in the prevention and treatment of diseases [12]. 'Functional foods' is an umbrella term that describes different foods or their bioactive ingredients which provide specific health-beneficial effects on

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consumption beyond their nutritional value [13]. Although the human lifespan has significantly increased in the past century owing to advances in medicine and lifestyle; the healthspan could not keep up the pace. Thus, while enhancing the lifespan may be a long-term goal; the healthspan must also be parallelly improved to maintain the quality of life [14]. However, aging itself is not a disease and as of now it cannot be eliminated or cured, but rather can only be managed. It is therefore conceivable that developing long-term preventive strategies which can help preserve cellular functional homeostasis in the wake of chronic stressors, can ultimately prevent or delay the onset or aggravation of age-related inflammatory pathologies and thus the aging phenotype. Functional foods and nutraceuticals represent a viable approach in this regard and thus not surprisingly, a novel discipline called 'nutrigerontology' has been envisaged to study the interrelationship between nutrition and aging [15,16]. In particular, a focus is now on the identification of nutritional geroprotector compounds that can alleviate the deleterious effects of aging both at the cellular and organismal level [17]. In the present paper, I intend to apprise the readers regarding the significance of cellular senescence in the aging process and then discuss evidence of how bioactive components present in foods can manage the different facets of cellular senescence. I also present a perspective on the emerging molecular targets of cellular senescence which could be useful for identifying novel nutraceuticals.

2. Cellular senescence in aging and disease

Cellular senescence was first discovered in fibroblast cells wherein it was demonstrated that proliferating mammalian cells have a finite replicative lifespan *in vitro* and thus are replicatively distinct from cancerous cells [18]. Recent studies have shown that cellular senescence is also active in non-proliferating post-mitotic cells such as cardiomyocytes [19], neuronal cells [20], and muscle cells [21] thereby suggesting a more comprehensive role of cellular senescence in the aging process than previously realized [22]. It is now understood that cellular senescence is a stress response mechanism that can be initiated in cells by exposure to a variety of cell intrinsic and extrinsic factors (Fig. 1). Three broad categories of cellular senescence are defined based on the type of induction: replicative senescence (telomere attrition),

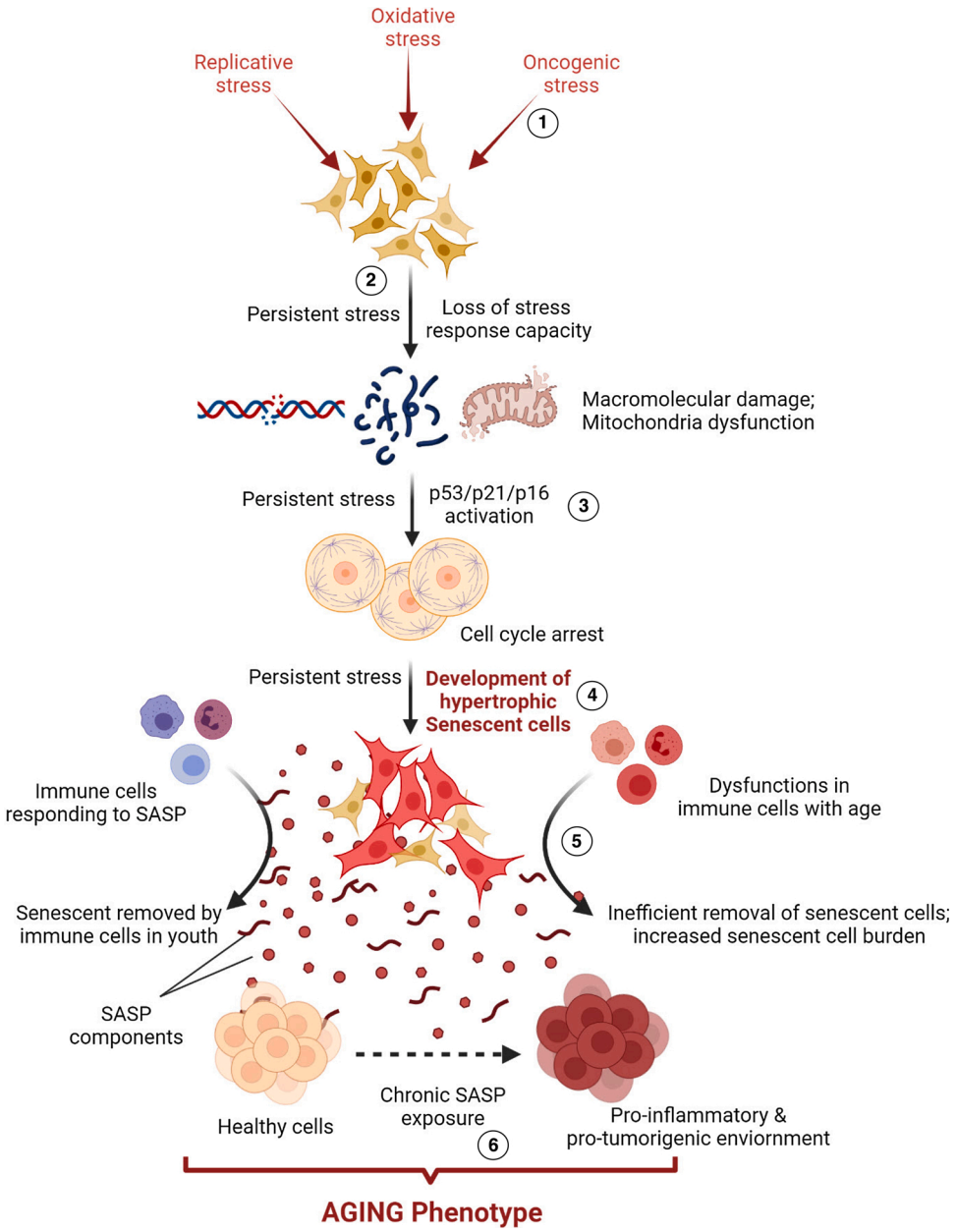

Fig. 1. Schematic illustration depicting the development of cellular senescence and its deleterious effects during aging. ***1***. Accumulation of chronic stressors and loss of stress response capacity overwhelms the cellular redox and metabolic homeostasis. ***2***. Persistent cellular stress result in macromolecular damage and organelle dysfunction leading to the induction of DNA damage response. ***3***. Accumulating macromolecular damage causes activation of cell cycle inhibitor pathways and the induction of cellular senescence. ***4***. In the presence of continued stress, the SASP develops, and ultimately cells acquire the complete phenotype characteristic of senescent cells. ***5***. Gradually, senescent cells start accumulating in tissues due to processes yet unclear, but likely to include phenomenon such as impaired immunosurveillance. ***6***. Ultimately, the increased senescent cells burden accompanied by the paracrine effects of the SASP, induce a pro-inflammatory and pro-tumorigenic environment in nearby healthier cells thereby causing tissue damage and predisposition to age-related diseases.

oncogene-induced senescence (activation of oncogenes), and genotoxic or oxidative stress-induced senescence [18,23,24]. However, it may be noted that the different types of cellular senescence are not mutually exclusive and cells may exhibit a senescent phenotype depending upon the type of stressor. Moreover, regardless of the different triggers of cellular senescence, SC are invariably accompanied by impaired mitochondrial functions, increased intracellular reactive oxygen species (ROS) production, oxidative stress, and activation of DNA damage response suggesting close molecular interlinks [25,26]. Besides, it has also been observed that oxidative stress can directly accelerate the fundamental cell-intrinsic stressor, i.e., telomere attrition, suggesting that oxidative stress-induced macromolecular damage may be a common denominator of the observed physiology of cellular senescence in different experiment settings [27,28]. Ultimately, depending upon the severity and persistence of the stress and cellular damage, cells may either enter cellular senescence (chronic stress) or apoptosis (acute stress), although the exact mechanisms, as well as the evolutionary significance of these cell fates, are still debatable [29–31].

SC are morphologically and physiologically distinct and are characterized by irreversible cell cycle arrest due to the activation of p53/$p21^{WAF1}$ and/or $p16^{INK4a}$/pRb pathways, DNA damage, chromatin remodeling, cellular hypertrophy, activation of SA-β-gal activity, altered metabolic and energetic pathways, resistance to apoptotic signaling, and redox stress, while late SC also exhibit characteristic secretion of a milieu of cytokines and growth factors called senescence-associated secretory phenotype (SASP) [32,33] (Fig. 1). It is crucial to consider that SC occur naturally and their presence *per se* is not considered of pathological significance since SC are critical for processes such as wound healing [34] and embryonic development [35]. The association between cellular senescence and aging was first realized when it was observed that SC accumulate with age in various tissues [36]. Recent research has shown that SC turnover not only decreases with time in the tissues of both animals and humans; the rate of SC accumulation is also tissue-dependent and non-linear which exponentially increases with advancing age [37–39]. This increase in tissue SC burden is significant and may drive organ dysfunctions as demonstrated in studies wherein transplantation of SC into healthy tissues induced disease-like condition and augmented the aging phenotype [40,41]. The specific reasons behind the apparent age-related accumulation of SC are not yet clear and may be related to the immune system. Cells of the immune system such as natural killer (NK) cells, macrophages, and CD8 T cells chemotactically respond to the inflammatory cytokines released by the SASP of SC and then recognize SC via specific immunogenic ligands which ultimately leads to immune cell-mediated cytolysis of SC [42] (Fig. 1). However, with advancing age, the immune system undergoes characteristic age-related dysfunctions collectively called immunosenescence, that may compromise the ability of immune cells to effectively clear SC [43]. Indeed, it was observed that impaired immunosurveillance due to defects in cytolytic properties of immune cells resulted in an increased accumulation of SC and inflammatory disorders *in vivo* [44]. Further, a recent study demonstrated that senescent immune cells are a causal determinant in driving the increased SC burden in tissues with aging [45]. It is thus not surprising that targeting immune cells for promoting efficient clearance of SC is rapidly emerging as an anti-aging strategy [43].

Age-related disorders are the main causes of morbidity and mortality in the elderly [46]. Accumulating data indicate that SC are directly associated with numerous yet pathogenetically distinct diseases suggesting that SC may be common drivers of organ dysfunctions and the diseased phenotype [47]. Recent discoveries have shown that SC are involved in the development of age-related disorders such as diabetes [48], cancer [49], obesity [50], pulmonary fibrosis [51], renal diseases [52], cardiovascular diseases [53], reduced tissue regenerative capacity [54], neurodegenerative diseases [55], metabolic dysfunction [56], hepatic steatosis [57], osteoarthritis [58], sarcopenia [59], and infections [60]. Conversely, removal or delayed development of SC confer decreased inflammatory stress, improved organ functions, attenuation of severity and progression of several age-related pathologies ultimately resulting in increased lifespan [47,61]. The role of SASP secreted by SC is of particular significance in the context of aging and disease. As SC steadily increase in tissues with age, the chronic presence of SASP can induce a pro-inflammatory and pro-tumorigenic environment which directly correlates with increased risk of inflammatory disorders in the affected tissues [62] (Fig. 1). Indeed, a recent study showed that SASP factors are positively correlated with chronological age and age-related health deficits in humans [63], while SASP from senescent fibroblasts promoted diseases such as cancer [64] and atherosclerosis [65]. Moreover, the pro-inflammatory nature of SASP appears to be associated with the phenomenon of inflamm-aging in elderly [66]. Inflamm-aging is a chronic, sterile, low-grade inflammatory state that ultimately contributes to the pathogenesis of age-related disorders [67,68]. Although the exact sources of inflamm-aging are yet unclear, however, SASP secreting SC as well as the aging innate immune cells are considered as potential candidates [69,70]. Taken together, it is reasonable to assert that age-related accumulation of SC is emerging as a single unifying factor underlying the process of aging as well as age-related disorders and thus signifies its therapeutic importance.

3. Management of cellular senescence: functional foods lead the way

Given the critical role of cellular senescence in aging and diseases, different strategies aimed at regulating the development of SC and SASP are increasingly becoming apparent [71] (Fig. 2). In modern times, a balanced nutritious diet and regular exercise are considered the most influential epigenetic factors that can augment healthy aging [72,73]. Numerous studies in animals and humans have demonstrated that consumption of foods rich in bioactive ingredients as well as specific probiotic bacteria can suppress cellular oxidative damage, improve organ functions, decrease mortality, and augment healthspan and lifespan [74–81]. Besides, functional foods and natural bioactive food ingredients have been consumed for centuries with little or no side effects and thus are ideal for long-term strategies necessary for attenuating chronic cellular stressors-mediated development of SC, SASP, and inflamm-aging [82–85]. I now deliberate various known and emerging nutrition-based targets and strategies for attenuating the effects of cellular senescence.

3.1. Major known nutrition-mediated anti-cellular senescence targets

3.1.1. Redox control and targeting cell cycle inhibitors

Deregulated ROS production and inflammatory stress can accelerate premature aging while the maintenance of cellular redox homeostasis

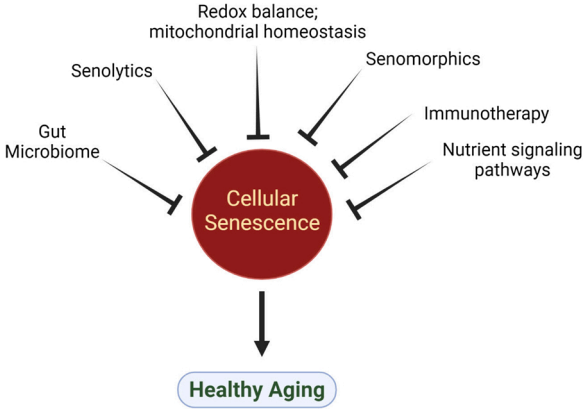

Fig. 2. Strategies and targets for the alleviation of cellular senescence and SASP.

and mitochondrial functions can strongly delay the onset of cellular senescence [27]. In this regard, it has been reported that organismal stress response capacity declines with age [86] which can be correlated with an increase in systemic age-related oxidative stress [87]. Notably, it was also demonstrated that increased oxidative stress burden can directly accelerate the development of cellular stress granules and establish a senescence program in different cells [88,89]. Further, it was reported that in the kidneys of mice deficient in antioxidant enzymes *(Sod1$^{-/-}$)*, a significantly increased oxidative damage accompanied by accelerated development of SC and SASP was evident thereby conclusively indicating the pivotal role of cellular redox system homeostasis in regulating cellular senescence-associated premature aging [90]. Nutritional status can be of particular importance in this context as several studies have shown that consumption of functional foods rich in potential nutraceuticals can improve systemic antioxidant capacity, alleviate oxidative stress and thus promote healthy aging in humans [91–95]. Indeed, numerous *in vitro* studies have demonstrated that bioactive components present in food can suppress multiple aspects of cellular senescence in varied cell types [96] (Fig. 3). For instance, we and others have previously observed that the bioactive green tea component epigallocatechin gallate (EGCG) can suppress the development of stress-induced premature senescence as well as replicative senescence characterized by decreased oxidative and inflammatory damage, and the inhibition of cell cycle inhibitors [97–99]. Similarly, resveratrol, another strong antioxidant, attenuated the stress-induced induction of cellular senescence in fibroblasts [100,101], nucleus pulposus cells [102], endothelial cells [103], adipose stem cells [104], and mesenchymal stem cells [105]. The phytochemical quercetin has also been shown to protect against cellular senescence in fibroblasts [106, 107] while the alkaloid berberine can ameliorate cellular senescence through the regulation of cell cycle inhibitors [108]. In addition to pure phytomolecules, studies have also identified medicinal plant extracts rich in potential nutraceuticals with anti-cellular senescence attributes mediated by improved redox homeostasis [109–111]. Similarly, marine omega-3-fatty acids [112], vitamin E [113], vitamin C [114], and minerals such as zinc [115] have also been implicated in the mitigation of stress-induced cellular senescence *in vitro*. Few *in vivo* studies have also demonstrated that consumption of bioactive food ingredients can reduce oxidative stress and SC burden. It was observed that resveratrol can attenuate high fat diet-induced oxidative stress and the development of vascular cell senescence by regulating Sirt1 expression in Wistar rats [116]. Similarly, quercetin has been shown to suppress the markers of high fat diet-induced cellular senescence in murine kidneys [117]. We have also observed that chronic consumption of EGCG across murine lifespan alleviated several deleterious aspects of cellular senescence in multiple animal tissues [118]. Together, there is reasonable evidence to consider that functional foods can protect against oxidative stress-induced cell injury and premature senescence, and clinical investigations into these observations are presently being envisaged [119].

3.1.2. *Senolytics and senomorphics*

One of the causes for the prolonged persistence of SC in tissues is their ability to resist apoptotic cell death due to the deregulation of anti-apoptotic and pro-apoptotic pathways. It has been demonstrated that targeted apoptosis of SC can attenuate age-related dysfunctions suggesting that strategies that can selectively remove SC are of considerable interest in reducing SC burden with age [120]. Natural and synthetic compounds, called 'senolytics', have been identified which can specifically ablate SC by inhibiting anti-apoptotic pathway (Bcl-2), and emerging early clinical trials are showing promising results of senolytics in improving age-related morbidity and mortality [121] (Fig. 3). The flavonoid quercetin was the first natural compound that showed senolytic potential [122], and since then, quercetin, in combination with the drug dasatinib has been identified as a potent senolytic recipe [123]. Recent studies have demonstrated that senolytic treatment with quercetin and dasatinib can decrease the numbers of SC, improve physical capacity, reduce SASP related pathologies, attenuate age-associated diseases such as obesity and lung fibrosis, and augment lifespan in rodents as well as humans [61,124–127]. In addition, few other dietary compounds such as tea catechin EGCG [97], flavonoid fisetin [128], alkaloid piperlongumine [129], curcumin [130], and olive-derived polyphenols [131] have also shown moderate senolytic attributes, and active research is currently underway to identify novel natural

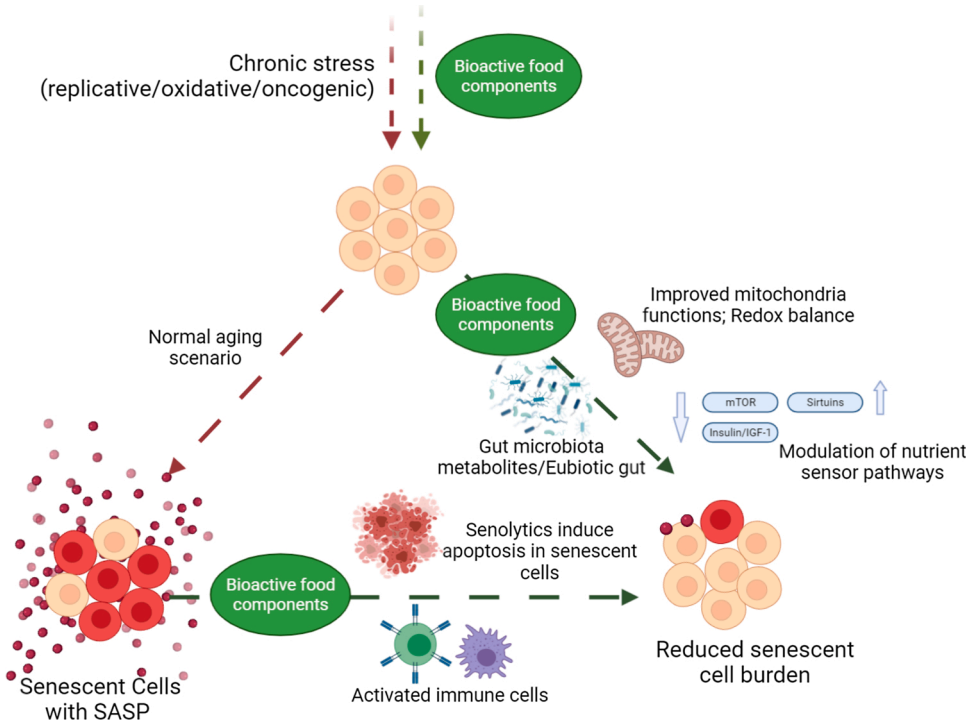

Fig. 3. Overview of functional food components mediated management of different aspects of cellular senescence. Bioactive food components can suppress redox stress, improve antioxidant capacity, alleviate SASP, modulate nutrient signaling pathways and improve the gut microbiome dysbiosis which may collectively reduce the senescent cell burden and senescent environment. In addition, bioactive food components can also alleviate immunosenescence and can directly ablate senescent cells through senolytic effects.

senolytics [132].

Despite their initial promising results, senolytics mediated global destruction of SC may have a downside as well since SC are also important in regulating processes such as tissue injury. In this context, we do not yet truly understand the ramifications of targeted SC removal on different physiological processes. As a result, perhaps it is more relevant to identify agents called 'senomorphics' that can alter the phenotype of SC by interfering with SASP and inflammatory pathways so that the deleterious paracrine effects of SC can be controlled. Given the known diverse antioxidant and anti-inflammatory attributes of various food ingredients; natural dietary compounds have been identified with the potential to alter SC phenotype but without cytolytic properties. An earlier study showed that plant flavonoids can suppress the SASP in senescent fibroblasts by targeting NF-κB and IκBζ signaling pathways [133]. Since then, several recent reports have demonstrated that phytomolecules such as EGCG [134], resveratrol [103], lycorine [135], alkaloid avenanthramice C [136], plant extracts rich in bioactive components such as Indian Hedgehog [137], and *Nephelium lappaceum* [138] as well as probiotic bacteria metabolites [139] can act as senomorphic agents by attenuating SASP and oxi-inflammatory stress through the inhibition of regulatory transcription factors and enhanced antioxidant defences. In addition, we observed that tea catechin EGCG can also protect immune cells from SASP-induced premature senescence *ex vivo* thereby suggesting that EGCG can help preserve immune functions during exposure to a chronic SASP environment [140].

3.1.3. Targeting nutrient-sensing longevity pathways

Nutrients are essential for appropriate cellular functions and growth. While excess nutrients result in anabolic cellular processes such as protein synthesis, a lack of nutrients stimulates catabolic functions such as autophagy to provide energy. These critical functions are regulated by coordinated interactions between various evolutionarily conserved nutrient signaling pathways. Interestingly, some of the nutrient sensors are also strongly implicated in organismal aging and longevity [141]. Examples of these nutrient-sensing longevity pathways include the mechanistic target of rapamycin (mTOR) pathway [142], sirtuins enzyme family [143], and insulin/IGF-1 signaling pathway [144]. Although the exact reasons underlying the relationship between nutrient-sensing pathways and organismal aging are yet unclear; it has been established that these pathways are impaired with age and that their molecular targeting can positively increase organismal healthspan and lifespan [145]. Unsurprisingly, the process of cellular senescence is also accompanied by deregulated nutrient signaling. This is because SC are under persistent stress and their metabolic profile is different from normal cells characterized by increased glycolysis and upregulated redox stress [146], enhanced mTOR activity [97,147], upregulated insulin/IGF-1 signaling [148,149], and suppressed sirtuins activity [150]. Moreover, there is evidence that pharmacological targeting of these nutrient signaling pathways can counter the different facets of cellular senescence (Fig. 3). The mTOR pathway coordinates eukaryotic cell growth and metabolism by enhancing anabolism and suppressing catabolism through the regulation of fundamental processes such as protein synthesis and autophagy [151]. SC are metabolically active and show upregulated mTOR activity which stimulates cell growth, but since SC cannot divide any further, the net result is cellular hypertrophy and strained redox processes because of excess metabolites and loss of autophagy [151]. It has been demonstrated that inhibition of the mTOR pathway is associated with anti-cellular senescence effects of various bioactive dietary components such as EGCG [97,134], resveratrol [152], berberine [153], curcumin [154], as well as probiotic bacteria metabolites [139]. Similarly, spermidine, an endogenous as well as plant-derived polyamine, has been shown to suppress mTOR signaling and augment autophagic response resulting in improved stress response and the inhibition of cellular senescence [155,156]. Sirtuins are a family (Sirt1-7) of nicotinamide adenine dinucleotide (NAD^+) consuming enzymes that are another major nutrient sensor involved in regulating organismal lifespan and health. Sirtuins enzyme activity (especially Sirt 1) decrease in SC [150,157], and inhibition of sirtuins promotes premature senescence in different cells [158–160]. Moreover, the coenzyme NAD^+, which is essential to sirtuin activity, also steadily declines with age resulting in further reduced sirtuins activity [161]. It is thus not surprising that upregulation of sirtuin expression or NAD^+ levels is associated with the inhibition of cellular senescence and enhanced lifespan. The pro-longevity attributes of few putative nutraceuticals have been attributed to increased sirtuins activity. Studies have shown that probiotic bacteria consumption can improve the healthspan and attenuate the severity of age-associated diseases by stimulating sirtuins activity [162–164]. Interestingly, a novel strain of probiotic bacteria *Lactobacillus acidophilus* NCFM with the ability to synthesize sirtuins was also identified suggesting potential role of microbial enzymes in supplementing sirtuins deficiency [165]. Similarly, phytomolecules such as resveratrol [166], EGCG [167], berberine [168,169], and curcumin [170] can also modulate sirtuins activity with age. Notably, it has also been observed that resveratrol can directly induce NAD^+ synthesis by stimulating activity of the NAD^+ synthetic enzyme nicotinamide mononucleotide adenylyl transferase thereby replenishing the age-related decline in NAD^+ levels and sirtuins function [171]. Activation of another nutrient sensing pathway insulin-IGF1 regulates organismal longevity through the suppression of FOXO transcription factors which are otherwise required for autophagy induction, apoptosis, redox stress and longevity extension [172]. It has been observed that probiotic bacteria, polyphenols as well as medicinal plant extracts can modulate insulin-IGF1 signalling resulting in enhanced oxidative stress response, improved autophagy and enhanced lifespan [173–180]. Taken together, it is evident that nutrient signalling longevity pathways are critical to the maintenance of cellular senescence, and identification of potential nutraceuticals targeting these pathways represent a promising anti-cellular senescence strategy.

3.2. Emerging anti-cellular senescence targets of bioactive food components

3.2.1. Gut microbiome modulation

The gut microbiota is rapidly evolving as a critical regulator of several facets of human health. Recent advances suggest a strong correlation between age-dependent changes in the composition of the gut microflora (gut dysbiosis), the development of chronic age-related disorders, and decreased lifespan [181,182]. Gut microbial secretory metabolites such as short-chain fatty acids (SCFA), amino acids, and polyamines are crucial in this regard due to their potent anti-inflammatory and anti-oxidative attributes as well as the ability to act at sites distal to the gut through peripheral circulation [183–185]. Evidence is emerging of an intricate relationship between the gut microbiome and cellular senescence [186]. For instance, it has been shown that altered gut microbiota components can contribute to SASP mediated inflammation and development of liver cancer [187] as well as the augmentation of immunosenescence [188] thereby suggesting that age-associated changes in the gut metabolome can promote the senescent environment. On the other hand, certain bacterial metabolites can also suppress premature stress-induced cellular senescence and SASP indicating that maintaining a healthy gut microflora dominated by commensal microbes may favourably affect the gut metabolome and prevent senescence [139,189]. Moreover, similar to other tissues, cells of the gastrointestinal tract also undergo cellular senescence and exhibit increased SC accumulation and SASP with age [37]. This senescence-associated tissue environment can impair immune responses in the gut and ultimately augment inflammatory disorders such as colon cancer [190]. Together, it is reasonable to assert that age-related alterations in the gut microbiota, development of cellular senescence, and senescence-associated diseases may be interlinked suggesting that strategies aimed at the maintenance of either of these factors may have mutualistic effects.

The gut microbiota is the first to interact with dietary components before the metabolites are assimilated into circulation. Nutritional factors, especially poorly absorbed compounds such as complex phytomolecules, are subject to extensive microbial biotransformation in the gut resulting in qualitative and quantitative changes in the metabolite profile [191,192]. It has also been observed that microbial fermentation of complex bioactive molecules often results in metabolites with superior biological effects [193]. Thus, in this perspective, it can be envisaged that the known health beneficial attributes (including the anti-cellular senescence effects) of dietary factors may be influenced by interactions/biotransformation within the gut microbiota itself. A recent study aptly demonstrates this fact wherein it was observed that the senolytic effects of dasatinib and quercetin are *essentially* mediated through reduced intestinal senescence, inflammation, and alteration of specific microbiota signatures in experimental aged mice [194]. Similarly, we also observed that consumption of green tea EGCG attenuated cellular senescence in multiple tissues of aging mice which correlated with changes in the gut microbiome [118]. These studies suggest a vital role of the gut microbiome in impacting the anti-cellular senescence effects of putative geroprotectors *in vivo* and thus gut microbiota modulation needs to be considered as an important regulator of functional foods mediated anti-senescence interventions (Fig. 3). In addition, interactions between the gut microbiota and dietary factors are also bidirectional wherein bioactive dietary ingredients such as polyphenols and probiotic bacteria can favourably modulate the structure and composition of the dysbiotic gut [195,196]. In fact, these observations have argued the development of novel phytomolecules-based second generation synbiotics that may also confer health beneficial effects during aging [197,198]. Thus, overall, it is reasonable to assert that nutritional factors and gut microbiota are mutually complementary which may beneficially affect human health and disease during aging.

3.2.2. *Immunomodulation and immunotherapy*

Bioactive nutritional ingredients are recognized for their immunomodulatory attributes and nutritional interventions are considered important tools in the adjunctive management of inflammatory disorders [199,200]. Increasing evidence suggests that phytomolecules, probiotics, fatty acids, vitamins, and minerals can beneficially regulate the aging immune response and counter immunosenescence [201]. In particular, several preclinical studies have shown that dietary supplementation of probiotic bacteria in aged experimental animals can augment cellular and humoral immune functions, alleviate inflamm-aging, and protect against infectious agents [202–207]. Similarly, clinical trials have also demonstrated that dietary consumption of probiotic lactic acid bacteria by healthy elderly can combat immunosenescence as evident from improved NK cell tumoricidal activity, the enhanced phagocytic response of granulocytes, increased CD4 + T cell proliferation as well as prevention of respiratory infections [208–212]. Apart from probiotics, age-related immunomodulatory effects have also been observed for plant secondary metabolites such as polyphenols [197,213–218], minerals such as zinc [219,220], omega-3-fatty acids [221–223], and vitamins [224,225]. However, evidence implicating an attenuation of SC burden mediated by improved immune functions owing to the consumption of functional foods is yet speculative. Our recent study observed that chronic consumption of tea catechin EGCG in mice decreased SC in multiple tissues which correlated with increased expression of early T cell activation marker (CD69) and suppression of inflamm-aging [118]. In another study, we demonstrated that treatment of EGCG can ameliorate the development of premature cellular senescence in murine macrophages exposed to secretory metabolites of senescent preadipocytes [140]. These observations provide tantalizing clues that nutrition-mediated effects on cellular senescence and SC accumulation could be related to their immunomodulatory properties (Fig. 3). However, further research exploring the relationship between functional foods, immunity, and cellular senescence is essential to comprehend the extent and depth of nutritional immunomodulatory effects in aging and disease [226].

4. Diet, cellular senescence, and aging

At present, calorie restriction (CR), defined as the reduction in average daily intake of calories without causing malnutrition, is considered the only reasonable effective model known to enhance longevity [227]. However, CR is not readily translatable to humans due to several factors, and thus alternate yet effective strategies are sought. In this regard, CR mimetics have been identified which are compounds that can provide health beneficial aspects of CR through the modulation of CR-related cellular pathways (such as mTOR and autophagy) but without following the stringent CR diet regimen [228]. Interestingly, several natural phytomolecules such as resveratrol, berberine, catechin, EGCG, quercetin, etc. have been recognized as potential CR mimetics indicating that dietary incorporation of sources of these bioactive compounds can favorably modulate the lifespan [228,229]. In the perspective of whole diets, a healthy diet plan should ideally protect against any malnutrition as well as the frequency and severity of non-communicable diseases such as diabetes, heart diseases, stroke, and cancer. Healthy aging diet plans such as Mediterranean diet, Okinawan diet, DASH diet, and Portfolio diet are characterized by high carbohydrate intake, low protein intake from sources such as vegetables, legumes, fish, and a fat profile rich in omega-3-fatty acids but limited in saturated fatty acids [230]. A growing relationship between dietary carbohydrate to protein ratio and lifespan has been observed. A high carbohydrate and low protein ratio ($\leq$ 10:1) diet can enhance the lifespan in a range of organisms [231,232], and in fact, this combination has been demonstrated to effectively recapitulate some of the health benefits of CR including systemic metabolic profile and brain aging [233,234]. Moreover, the sources of proteins and fats in the diet also determine the health beneficial merits of the diet. For instance, in a prospective cohort study, it was observed that proteins/fats derived from plant-based sources such as vegetables, nuts, peanut butter, and whole-grain bread, were associated with lower all-cause mortality in the elderly [235]. In addition, clinical trials have shown that a Mediterranean diet regimen can influence the markers of cellular senescence [236]. As an example, consumption of a Mediterranean diet for 4 weeks by healthy elderly reduced the numbers of human endothelial cells with higher intracellular ROS production, cellular apoptosis, and shortened telomeres [237]. Similarly, in a recent study, coronary heart disease patients fed with a Mediterranean diet demonstrated higher proliferation and angiogenesis, suppressed apoptosis, intracellular ROS production, and senescence in endothelial cells suggesting a better balance of vascular homeostasis in patients with coronary heart disease [238]. In addition, a positive correlation between consumption of the Mediterranean diet and cellular telomere length has been demonstrated in meta-analyses observations [239,240]. Taken together, it is reasonable to assert that a dietary regimen rich in high carbohydrates to protein ratio and diverse sources of proteins can mitigate different aspects of stress and cellular senescence ultimately improving the healthspan and lifespan akin to CR.

5. Limitations and challenges of functional foods as viable modulators of cellular senescence

As highlighted in this manuscript, there is a strong rational basis to assert that functional foods and potential nutraceuticals can modulate the various aspects of cellular senescence. However, it is also apparent that at present, the experimental evidence available to support these assertions is largely based on *in vitro* studies while few *in vivo* investigations are also available. On the other hand, except for preliminary reports based on selected natural senolytics and sporadic observations on the consumption of the Mediterranean diet; there are virtually no clinical data that specifically and holistically test the health beneficial effects of functional foods during aging through the purview of cellular senescence and SASP. This is crucial since dietary components

as well as nutraceuticals have been documented to improve the markers of aging in humans, and yet the causal relationship linking their health beneficial effects with the process of cellular senescence remains to be conclusively elucidated. In addition, our knowledge regarding the mechanisms and impact of cellular senescence is still evolving and as novel molecular targets of cellular senescence are identified, exploration of nutraceuticals, food components, or medicinal plants as anti-cellular senescence agents would gradually become more desirable as also highlighted in this manuscript. However, there is a need for cautious interpretation of preliminary and exploratory studies, especially related to the *in vitro* evidence, for developing subsequent *in vivo* and clinical investigations since several complex and variable factors such as dose, bioavailability, and physiological relevance significantly impact the biological effects and observations of the test compound. As a case in point, plant polyphenols have been asserted with a variety of health beneficial effects *in vitro*, and yet there is ample ambiguity on their source, amount, and mode of delivery applicable for reaching a desired effect across the genetically varied human population groups [241,242]. Moreover, it is also pertinent to mention that functional foods and nutraceuticals should be considered as viable approaches to 'delay' or 'manage' the deleterious effects of cellular senescence, and it may be unpragmatic or even undesirable (given the known essential role of SC in biological processes) to assert nutraceuticals with complete cellular senescence regressive properties. Taken together, it is rational to suggest that although there is enough evidence to explore diet as a modulator of cellular senescence (Fig. 4) but a cautious and critical approach is prudent for meaningful clinical translation(s).

6. Conclusions and future directions

The research into the biology of aging is at an interesting juncture today wherein tangible molecular targets of cellular aging are being increasingly identified. A wealth of data demonstrates that accumulation of SC is a critical factor preceding aging and age-related disorders, and strategies aimed at the removal or the management of the deleterious SC phenotype are of considerable interest. However, our knowledge of cellular senescence and its impact on aging and disease is still evolving and incomplete. In particular, a more integrative understanding of cellular senescence vis-à-vis the immune system is required to decipher how SC communicate with the host immune cells. This is especially relevant since a recent study has shown that SC can develop autonomous immune evading features which enhance their persistence in tissues [243]. Similarly, how cellular senescence in the immune cells *per se* impacts their biological functions is only beginning to be understood [244]. In addition, the relationship between age-related alterations in the gut microbiome and cellular senescence is not fully understood. Novel gut metabolome-based high throughput strategies are suggested for functional annotation of the gut microbiome with cellular senescence [245]. Nutrition is the single most impactful non-genetic factor governing human health during aging. Given the emerging cellular senescence-centric paradigm of aging, nutritionists and biogerontologists must strive to assess the age modulatory aspects of nutraceuticals within the purview of cellular senescence and SASP. In this context, there is compelling evidence that nutritional factors can mitigate the different facets of cellular senescence, although more information on immunotherapy, senomorphics, and gut microbiota modulatory aspects of nutraceuticals is especially desired. These avenues may ultimately help understand the mechanism(s) of nutraceuticals, and may also aid in the development of nutrition-oriented healthy-aging therapies.

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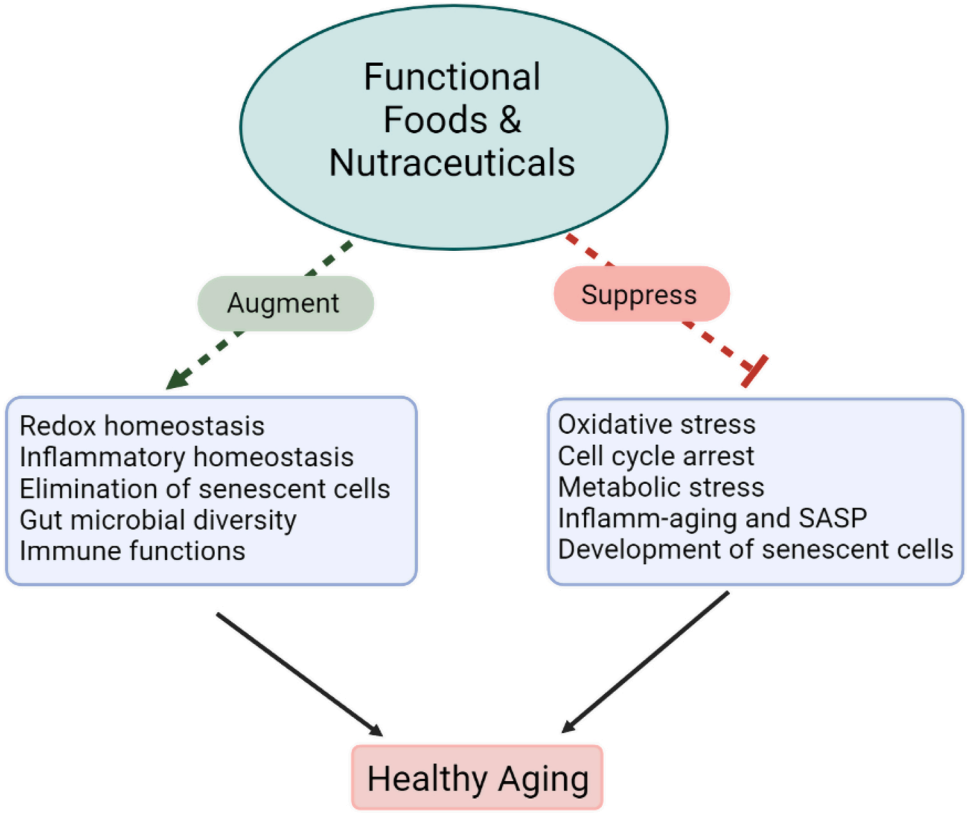

Fig. 4. Potential biological effects of bioactive food components in alleviating the deleterious aspects of cellular senescence and augmentation of healthy aging.

Declaration of Competing Interest

The authors report no declarations of interest.

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