Food for healthier ageing: Power on your plate

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Abstract

Inflammageing is a persistent low-level inflammatory burden that accompanies age-related dysregulation of the immune system during normative ageing and within the diseasome of ageing. A healthy diet containing a balanced amount of macronutrients, vitamins and minerals, adequate in calories and rich in poly(phenols), has an essential role in mitigating the effects of inflammageing and extending healthspan through modulation of the activity of a range of factors. These include transcription factors, such as nuclear factor erythroid-derived 2 related factor 2 (Nrf2) and nuclear factor-κB (NF-kB), the inflammasome and the activities of the gut microbiota. The aim of this narrative review is to discuss the potential of food to ameliorate the effects of the diseasome of ageing.

Keywords: inflammageing, nutrition, food, inflammation, senescence.

Introduction

Ageing is a time-dependent, multi-factorial biological process that facilitates a progressive physiological deterioration across organ systems, leading to multiple dysfunctions (P. G. Shiels et al. 2017; Maduro, Luís, and Soares 2021). All physiological functions are interconnected and perturbed during the ageing process, including both the structure and microbial composition of the gut, the activity of the immune system, antigen-induced proliferation, mitochondrial activity and regulation of the epigenetic landscape. Chronological age is involved with the chronic burden of lifestyle diseases, such as cancer (De Magalhães 2013), neurodegenerative diseases (Hou et al. 2019), cardiovascular diseases (CVD) (Mozos et al. 2021), metabolic syndrome (Yu et al. 2020) and chronic kidney disease (CKD) (Kooman et al. 2014; Stenvinkel and Shiels 2019).

Ageing can be characterised by a range of hallmarks such as genomic instability, mitochondrial dysfunction, telomere attrition, and loss of proteostasis, among others that are common across taxa, indicating that the associated underlying fundamental biological processes are critical to how physiological deterioration occurs and progresses (López-Otín et al. 2013; P. G. Shiels et al. 2019). Targeting these hallmarks, using a range of natural and synthetic agents provides a template for preventing a host of multiple age-related diseases (Kooman et al. 2014; P. Shiels and Ritzau-Reid 2015; Maduro, Luís, and Soares 2021; Shannon et al. 2021).

Most age-related chronic diseases in mammals share similar features, including decreased Nrf2 expression, oxidative stress, mitochondrial dysfunction, metabolic imbalance, cellular senescence, tissue hypoxia, gut dysbiosis and chronic low-grade inflammation (inflammageing) (Koppula et al. 2021; P. G. Shiels et al. 2019). Inflammageing is related to complex biochemical pathways altered during ageing and inherent within the diseasome of ageing, which includes chronic diseases that accumulate with age such as CKD (Kooman et

al. 2017; Franceschi et al. 2018; Ferrucci and Fabbri 2018). Inflammageing is also an inherent feature of immunosenescence, which is characterised by loss of energy and the accumulation of memory T cells. It is accompanied by hallmarks of normative ageing, including telomere attrition, epigenetic dysregulation and accumulation of senescent cells (Weyh, Krüger, and Strasser 2020; Y. J. Kim et al. 2015; P. G. Shiels et al. 2017). However, physiological ageing and its molecular and cellular components do not fully explain immunosenescence.

Increased longevity and longer healthspan are more prevalent in certain parts of the world. Five regions of the world, including Okinawa (Japan), Sardinia (Italy), Nicoya Peninsula (Costa Rica), Ikaria (Greece) and Loma Linda (California), have been named "blue-zones", a term for a place or region with a high percentage of people who have reached an age >100 years, without diseases or age-related complications when compared to other areas of the world (Buettner 2015; Poulain et al. 2021). This difference in health and life span between populations, observed even in monozygotic twins, has been linked to specific exposome factors (P. G. Shiels et al. 2021), such as diet and socioeconomic position and lifestyle. Only three exposome factors, tobacco smoking, air pollution and diet, have been responsible for approximately 50% of annual global deaths (Lim et al. 2012; Afshin et al. 2019). Of these exposome factors, an unhealthy diet appears to be the strongest lever for affecting morbidity and mortality (Willett et al. 2019). Indeed, diet toward a healthy pattern such as DASH, Mediterranean diet, Japanese cuisine-based DASH and cuisine-based Chinese healthy diet improves the health status (Umemoto et al. 2022).

In keeping with the ancient adage "*let food be their medicine*", a misquote of the Greek physician and philosopher Hippocrates (460BC-370BC), 2500 years later, this thesis has been supported by results from the Global burden of disease study (Afshin et al. 2019). This landmark study has shown that unhealthy diets, characterised by a high intake of sodium and

sugar, and a low intake of vegetables, fruits and whole-grain, contribute to most of the burden of lifestyle diseases within the diseasome of ageing (Stenvinkel and Shiels 2019).

This narrative review will now discuss the mechanistic pathways through which food can be used as medicine to prevent or treat the diseasome of ageing. It will describe potential interventions concerning specific hallmarks of ageing and two classical features of mammalian ageing (gut dysbiosis and diminished Nrf2 expression), which are expected within the diseasome.

Drivers of cellular Senescence and Inflammageing

Senescence is derived from the Latin "senex", meaning "old". First described by Hayflick and Moorhead (1961)(Hayflick and Moorhead 1961), cellular senescence is a state of growth arrest, accompanied by specific changes in chromatin organisation, gene transcription and protein secretion resulting from DNA and mitochondrial damage. There is no gold-standard biomarker to characterise what constitutes cellular senescence. However, cyclin-dependent kinase inhibitor 2A (CDKN2A) transcriptional expression (in chromosome 9p21) that encodes proteins $p16^{ink4a}$ (Krishnamurthy et al. 2006) has proven to be a consistent feature of cells in stable growth arrest, a characteristic of senescent cells. Typically, this is accompanied by increased expression of lysosomal senescence-associated β-galactosidase activity (SA-β-gal)(Dimri et al. 1995), since in senescent cells, the lysosomal biogenesis is increased due to the increased expression of gene *GLB1*, which encodes the lysosomal enzyme.

Senescence can be induced by a range of stressors, including internal and external sources of reactive oxygen species (ROS) such as ionising and UV radiation, environmental toxins, oncogenic, genotoxic chemicals, and heat shock, among others that activate both $p16^{ink4a}$ and $p14^{ARF}$ expression. $P14^{ARF}$ is a nuclear tumour suppressor protein located within the CDKN2 locus that binds to ubiquitin ligase, which ubiquitinylates p53 (a tumour

suppressor) for proteasomal degradation and induces apoptosis. The $p16^{ink4a}$ protein prevents the phosphorylation of the retinoblastoma tumour suppressor protein (Rb), blocking the activity of CDK4/CDK6 (kinases that promote the Rb phosphorylation and are critical for cell cycle progression). Thus, $p16^{ink4a}$ and $p14^{ARF}$ are upregulated in senescent cells and are hallmarks of ageing, contributing to the cell cycle arrest (Leon et al. 2021; Dimri et al. 2000; Ziegler, Wiley, and Velarde 2015; D. Zhu et al. 2002).

Senescent cells (SC) release a cocktail of pro-inflammatory cytokines as part of a senescence-associated secretory phenotype (SASP), or secretome responsible for "bystander effects", which poison the surrounding tissue and promote dysfunction. This contributes to inflammation, stem cell exhaustion and modification of cells in the immune system. The latter includes T- and B-lymphocyte responses, granulocyte and macrophages activity, reduction of hematopoietic tissue and secretory IgA, oxidation of polyunsaturated fatty acids in the membrane of immune cells and impaired phagocytosis (Ferrucci and Fabbri 2018; Franceschi et al. 2018; Robinson et al. 2013; Wiley et al. 2017; McHugh and Gil 2018; Abiri and Vafa 2020).

SASP production (chemokines, proteases, cytokines) is stimulated by many pathways, including the p38, p53 and MAPK pathways and non-coding RNAs regulators. Inflammageing also intersects with a range of senescence-associated features, such as nuclear factor-κB (NF-κB) signalling and the Nod-like receptor pyrin domain containing 3 (NLRP3) inflammasome, both of which contribute to age-related inflammatory burden (Chan and Schroder 2020; L. Alvarenga, Cardozo, Borges, et al. 2020).

ROS and the SASP stimulate a feedback loop that results in increased ROS production, mostly in the mitochondria, elevating the intracellular ROS and facilitating the development of a senescent phenotype through telomere nucleoprotein complex dysfunction (Ziegler, Wiley, and Velarde 2015). Telomeres are nucleoprotein structures rich in guanine bases that

can act as a sink for scavenging reactive oxygen species (ROS), thus mitigating oxidation and DNA damage (Freitas-Simoes, Ros, and Sala-Vila 2018). Telomere shortening occurs in every cell division cycle in primary somatic cells (Sanders and Newman 2013). Telomere shortening progresses with age advanced and has been reported to shorten in multiple human cell types from 11-15kb in youth to 4-7kb in the elderly (Chandrasekaran, Idelchik, and Melendez 2017). The rate of telomere shortening is usually accelerated with the disease. Despite some questions regarding whether telomere shortening is a reliable biomarker of ageing, it remains widely used as an important biomarker; however, methods to evaluate it should be improved (Vaiserman and Krasnienkov 2020). **Figure 1** depicts biological mechanisms involved in cellular senescence.

With increasing age, the capacity to mitigate the effects of the accumulation of senescent cells relates to a loss of the maintenance of physiological homeostasis. This results in loss of physiological function as a reflection of the burden of wear and tear (i.e., allostatic (over) load) before the onset of the diseasome of ageing is eventually facilitated. The biochemical pathways altered during the ageing process associated with inflammation result in the production of a low-grade, chronic sterile inflammatory phenotype, termed 'inflammageing', which is a component of many chronic diseases (Kooman et al. 2017; Ferrucci and Fabbri 2018). Also, inflammageing is closely associated with gut membrane barrier integrity and gut microbiota composition (Kühn et al. 2020; Takiishi, Fenero, and Câmara 2017; Larrick and Mendelsohn 2020).

The gut microbiota and the diseasome of ageing

Ageing sees a general reduction in levels of *Bacteroidetes, Tenericutes* and *Bifidobacteria* in the gut and an increase in *Firmicutes* and *Actinobacteria*; increasing the Firmicutes to Bacteroidetes ratio (Fransen et al. 2017; Thevaranjan et al. 2017). In

general, lower microbial diversity and relative abundance accompany ageing (Claesson et al. 2012; Santoro et al. 2018). A reduction in saccharolytic bacteria and an increase in proteolytic bacteria, along with increased colonisation by pathobionts, is linked to inflammageing through increased toxin production and generation of lipopolysaccharides (LPS) (Rampelli et al. 2013). Inosine (a metabolite that regulates mucosal and systemic immune cells) is produced by specific gut microbiota, which links microbe-induced metabolite synthesis and the efficacy of immunotherapy (Mager et al. 2020). A recent meta-analysis with metagenomics datasets to evaluate possible interactions between age and the microbiome in different diseases concluded that age is a major confounder in studies linking the microbiome to disease (Ghosh et al. 2020).

As the gut microbiota changes with ageing and/or disease, toxins produced by the gut microbiota, such as indole-3-acetic acid (IAA), indoxyl sulfate (IS), p-cresyl glucuronide, p-cresyl sulfate (PCS), phenylacetylglutamine (PAG) and trimethylamine N-oxide (TMAO) accumulate. Moreover, the altered microbiota leads to increased production of LPS, systemic endotoxemia and reduced short-chain fatty acid (SCFA) production, contributing to inflammageing (O'Toole and Shiels 2020; Thevaranjan et al. 2017; Fransen et al. 2017; D. Mafra et al. 2019). Among these microbially generated toxic metabolites, TMA (W. Zhu et al. 2016) and PAG (Nemet et al. 2020) have received much recent interest as they promote CVD and thrombotic risk. Since the susceptibility to atherosclerosis is transmitted via gut microbial transplantation, gut microbes may represent a novel therapeutic target for modulating the risk of atherosclerosis (Gregory et al. 2015).

Inflammation *per se* can also cause changes in the gut microbiota composition, reducing the abundance of strict anaerobic Firmicutes and increasing the prevalence of "pathobionts" in the gut (Santoro et al. 2018; Candela et al. 2014). Indeed, germ-free mice transplanted with gut microbiota from old mice presented an increased inflammation burden

(Fransen et al. 2017; Thevaranjan et al. 2017), supporting this thesis. LPS and toxins produced by the microbiota can activate NF-κB and $p16^{ink4a}$ expression (K. A. Kim et al. 2016), contributing to cellular and physiological senescence. A recent study in a mouse model of kidney disease has shown that dietary changes led to the posttranslational modification of microbial proteins that reduced the generation of uremic toxins (Lobel et al. 2020). Thus, the functional processes that underlie the interactions between the host and the microbiota need more attention.

While there is a shift in the microbiota to a more "pathobiont profile" in old age, this can be counterbalanced by other microbes generating a lower potential pathobiont profile and maintaining a good "mutualistic pact" in extreme longevity (such as in people 105-109 years old), (Santoro et al. 2018; Biagi et al. 2016) (**Table 1)**. These changes are related to good immunological health, the energy source of colonocytes, lean body mass and superior lipid profile and metabolic system (Kong et al. 2016; Moraes, Borges, and Mafra 2016; Schnorr et al. 2014; Tuikhar et al. 2019).

Intestinal alkaline phosphatase (IAP), expressed in the apical microvilli of the brush border of enterocytes, also has an essential role in the gut (L. Alvarenga, Cardozo, Lindholm, et al. 2020). Kühn *et al.* (2020)(Kühn et al. 2020) have reported that mice supplemented with IAP had an altered microbiota associated with reduced frailty, improved gut barrier dysfunction, reduced endotoxemia and inflammation, critically, increased lifespan. Preservation of barrier function (preserved by ZO-1 and occludin proteins) is involved in slowing the ageing process and reduction of inflammageing, as the reduction in its activity leads to increased gut permeability, increasing levels of pro-inflammatory metabolites, such as LPS, flagellin and toxins produced by the gut microbiota (Kühn et al. 2020; Takiishi, Fenero, and Câmara 2017; Larrick and Mendelsohn 2020). Whereas the gut microbiome contributes to the generation of pro-inflammatory metabolites, dysbiosis can also influence

metabolism and reduce the production of short-chain fatty acids (SCFAs), such as butyrate. Reduction in SCFA production has been linked to exacerbation of inflammageing (**Figure 2**).

Nrf2 expression and the diseasome of ageing

As an endogenous antioxidant system, the Nrf2-Kelch-like-ech-associated protein 1 (Nrf2-Keap1) signalling pathway is critical for cytoprotection. In response to cytostressors, there is a conformational change in the structure of the cysteine-containing regions in the Keap1 (a protein with 627 amino acid and possess five domains) in the cytoplasm. Then, Nrf2 is translocated to the cell nucleus and heterodimerises with the small musculoaponeurotic fibrosarcoma (sMaf) proteins (leucine zipper-type transcription factors) that bind to antioxidant response elements (AREs) in the DNA and increase the gene expression of more than 250 genes involved with the synthesis of antioxidants such as several glutathione S-transferases, catalase, superoxide dismutase, NAD(P)H quinone-oxidoreductase-1, heme-oxygenase-1 genes. Several glycolytic enzymes (glucose phosphate isomerase, hexokinases, 6-phosphofructo-2-kinase, etc.) and enzymes involved in the pentose phosphate pathway (glucose-6-phosphate dehydrogenase and phosphogluconate dehydrogenase) are regulated by Nrf2. Also, Nrf2 is involved with the activation of the purine biosynthesis pathway (phosphoribosyl pyrophosphate amidotransferase and methylenetetrahydrofolate dehydrogenase 2) and enzymes involved with iron and lipid metabolism, as well as enzymes responsible for unfolded protein response and proteostasis (Hayes and Dinkova-Kostova 2014. He, Ru, and Wen 2020). As a result, cytoprotective gene networks are activated to combat stress.

Ageing, however, is associated with reduced expression of Nrf2, which enables genomic instability, disruption of proteostasis and prevents the mitigation of oxidative stress, thus linking Nrf2 to hallmarks of ageing (P. G. Shiels et al. 2019).

Studies in laboratory models and non-human primates have shown impaired ability to stimulate an effective Nrf2-dependent antioxidant defence with increasing age in response to oxidative stressors resulting in increased oxidative damage in aged cells (Csiszar et al. 2012; Ungvari et al. 2019). A previous study has demonstrated age-associated functional decline resulting from a progressive loss of the ability to activate Nrf2 targets in response to acute exposure stress (Rahman et al. 2013). The role of Nrf2 in ageing is also seen in compelling evidence that demonstrates increased sensitivity to carcinogens and rapid organ damage in mice lacking the Nrf2 gene (Cuadrado et al. 2019; Stenvinkel and Shiels 2019). Studies in Caenorhabditis elegans have also linked the Nrf2 functional ortholog- Skinhead-1 (SKN-1) as a crucial participant in the homeostatic function that elicits a significant effect on life and healthspan in mammals (Blackwell et al. 2015). Interestingly, these mammalian observations are supported by an also observed in Drosophila.

A common feature of many species living in stressful environments is an upregulation of Nrf2 expression or an increase in its coding capacity (Vázquez-Medina et al. 2013), suggesting a cytoprotective activity in extreme living conditions. This can be observed in species such as the hibernating ground squirrel (Ictidomys tridecemlineatus), deep-diving seals and the naked mole-rat (P. G. Shiels et al. 2019).

Can Food be used as medicine to combat inflammageing?

Nutritional interventions using the concept of 'Food as Medicine' (Denise Mafra et al. 2021) provide important insights into how food can modulate transcription factors such as Nrf2 and mitigate the inflammatory burden and physiological deficits associated with ageing.

Food is one of the most critical determinants of healthspan, as it is central to ROS production, the generation of metabolic stress, and inflammatory and immune processes

(Abiri and Vafa 2020). Indeed, an unhealthy diet (e.g., containing ultra-processed food, processed meats, biscuits, margarine) is associated with accelerated biological ageing and reduced health span (Alonso-Pedrero et al. 2020; Rafie et al. 2017).

Epigenetic diet

A range of diets has promoted age-related health, including an 'Epigenetic diet' (Blasiak et al. 2020; Franzago et al. 2020). Such epigenetic diets include increased consumption of foods containing isothiocyanates, folic acid, vitamin B12, choline, and betaine to enhance the maintenance of the epigenome, as shown in **Table 2** (Cardozo et al. 2020; Denise Mafra et al. 2021). While intuitive, their efficacy remains to be proven.

The effect of an epigenetic diet consisting of high consumption of methyl donor foodstuffs (folic acid, vitamin B12, choline and betaine) has been investigated in the Agouti viable yellow (Avy) mouse model. In this model, altering maternal nutrition by ensuring higher consumption of methyl donor group foodstuffs resulted in variation of offspring coat colour, a direct consequence of its epigenetic regulation. The offspring manifested leaner body weight, darker furs and increased resistance to diseases than untreated Avy mouse controls (Waterland and Jirtle 2003).

Hypomethylation of different families of repetitive sequences, such as LINE elements in man, has been observed in a range of human diseases, indicating that their methylation status contributes to ageing and healthspan (Pappalardo and Barra 2021).

Consistent with the above thesis, an 'epigenetic diet' has been shown to impact the methylation status of LINE-1 elements in a study of young cancer-free women, where participants with a poorer dietary lifestyle, characterised by lower consumption of fruits, vegetables and folate intake displayed LINE hypomethylation in blood leukocytes compared to women with median adherence to an epigenetic diet (Agodi et al. 2015). A similar study in men aged 55-80 years and women aged 60-80 years using diets rich in folates and

isothiocyanate observed upregulation of 8 genes: EEF2, COL18A1, IL4I1, LEPR, PLAGL1, IFRDI, MAPKAPK2 and PPARGC1B involved in the regulation of inflammation and immunocompetence (Marques-Rocha et al. 2016).

A recent epigenome-wide analysis (EWAS) of methylation at >400,000 CpG sites in five cohorts has identified methylation levels at 30CpG to correlate with habitual consumption of components of an 'epigenetic diet'(Ma et al. 2020), in keeping with health benefits from using food as medicine.

In a recent pilot study, a 1-year dietary intervention using the Mediterranean diet (MedDiet) was reported in ***epigenetic rejuvenation*** when estimating DNAmAge using data for methylation at 353CpG sites in genomic DNA. This, however, remains to be replicated and is open to the effects of a range of confounders such as lifestyle (Gensous et al. 2020). The potential effects of an epigenetic modulating diet on epigenetic mechanisms are shown in **Figure 3**.

Food restriction as a therapy

Caloric restriction (CR) is an established approach in animal models to prevent the accumulation of senescent cells (M. B. Lee et al. 2021; Maduro, Luís, and Soares 2021). Although the specific molecular mechanisms related to the benefits of CR are not yet evident, some pathways have been related, such as activation of AMP protein kinase (AMPK) and sirtuins (SIRTs), inhibition of insulin-like growth factor-1 (IGF-1) signalling, fibroblast growth hormone factor 21 (FGF21) and mechanistic target inhibition of rapamycin (mTOR) (M. B. Lee et al. 2021; Maduro, Luís, and Soares 2021). Critically, CR and dietary restriction can upregulate the trans-sulphuration pathway (TSP), resulting in the production of H_2S, which induces Nrf2-mediated cytoprotection and results in more efficient mitochondrial function (Hine et al. 2018). Studies evaluated metabolic health and longevity in male and female C57BL6 mice that consumed different proportions of dietary

macronutrients ad libitum: protein (5–60%), fat (16–75%), carbohydrate (16–75%) and energy (8, 13 or 17 kJ/g of food) – and found that low-protein and high-carbohydrate diets resulted in greater longevity (Solon-Biet et al. 2014; Solon-Biet et al. 2015).

Many fad diets have involved caloric restriction, such as low carb diets or ketogenic diets, protein restrictions or specific amino acid restriction diets, and the celebrated intermittent fasting diet. All are known to reduce weight in obese people. However, there is no solid scientific evidence of their effects on biological ageing in humans (M. B. Lee et al. 2021).

Diet restriction has been a common human practice across numerous cultures for centuries. Cumulative results from observational and randomised clinical trials suggest that the benefits of CR in humans result in the same metabolic and molecular adaptations that have been shown to improve health and delay the accumulation of molecular damage in animal models of longevity. Moderate CR in humans seems to favour metabolic and hormonal situations implicated in the pathogenesis of type 2 diabetes (T2D), CVD and cancer, the leading causes of morbidity, disability and mortality (Most et al. 2017). CR appears to have an anti-inflammatory effect in humans, protecting against atherosclerotic risk factors and resulting in less carotid intima-media thickening. In addition, others responsible for this caloric restriction-mediated anti-inflammatory effect include reduced adiposity and reduced secretion of pro-inflammatory cytokines (Fontana et al. 2007; Fontana 2009; Fontana et al. 2004). The CALERIE-2 Study (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) evaluated healthy non-obese adults who underwent caloric restriction (25%) continuously for two years and demonstrated beneficial effects on the body and regional adiposity, which could facilitate healthspan (Das et al. 2017).

The effects of CR can also be achieved using mimetics, as shown in **Table 3**, to mitigate inflammation and oxidative stress (Denise Mafra et al. 2021; Shankar et al. 2017; J. Zhang

et al. 2019; Bai and Wang 2019; Esmaeil et al. 2017; Livia Alvarenga et al. 2020; A. Wang et al. 2019; Zhao and Zhang 2020; Barreca et al. 2014; Chauhan, Jang, and Kim 2020; Ribeiro et al. 2021; De Almeida Alvarenga et al. 2019; Yang et al. 2018; Limtrakul et al. 2016; Sun, Jin, and Shi 2017; Golovinskaia and Wang 2021).

Food as senotherapy

Numerous bioactive compounds and nutrients in the foodome can act as senotherapeutics, i.e., agents that combat physiological decline with age, combat disease and act as cytoprotective agents, with the potential to mitigate inflammation. In particular, they act as agonists for Nrf2, which activates hundreds of anti-inflammatory and anti-oxidative genes (Ebert et al. 2020; Arefin et al. 2020). For example, cruciferous vegetables, tomato skin, red-purple plants, coffee beans, rosemary and turmeric contain bioactive compounds, including Nrf2 agonists, such as sulforaphane (SFN). Moreover, as these foods neutralise NF-κB-driven inflammatory response, they can mitigate the inflammatory and pro-oxidative inflammageing phenotype (Denise Mafra et al. 2021). In a 2019 bibliometric analysis of various natural Nrf2 agonists, resveratrol, curcumin, and SFN emerged as the most clinically relevant. This could be linked to its lipophilic nature and low molecular weight, ensuring bioavailability. The oily sulfur-isothiocyanate sulforaphane (SFN), found in cruciferous vegetables, such as cabbage and broccoli, particularly broccoli sprouts, is a potent inductor of Nrf2 (Cardozo et al. 2020). Although the primary mechanism proposed for SFN´s health benefits is via activation of Nrf2, it also inhibits NF-kB expression (Cardozo et al. 2020; Dong et al. 2016) and suppresses NLRP3 activity (Gong et al. 2019).

Another bioactive Nrf2 agonist is the phenylpropanoid cinnamaldehyde found in cinnamon, chocolate, tomatoes, and citrus food (P. Wang et al. 2020). Polyphenols found in fruits and vegetables can interact with cysteine residues in Keap1, causing it to disassociate

from Nrf2, enabling its translocation to the nucleus (Denise Mafra et al. 2021). Quercetin can also increase Nrf2 expression by inhibiting the proteasomal degradation pathway, allowing the release of Nrf2 from the Keap1 repressor to the nucleus (Nabavi et al. 2016).

Several constituents in fruit and vegetables have distinct geroprotective properties. Fisetin is a flavonoid found in strawberries, mangoes, apples, grapes, onion, persimmon and cucumber (at concentrations between 2-160 µg/g) that induces apoptosis of senescent cells and has an anti-inflammatory property (Yousefzadeh et al. 2018; Y. Zhu et al. 2017). In a rat model of D-galactose (D-gal)-induced accelerated senescence, fisetin treatment reduced both age-induced eryptosis processes and oxidative stress (S. Singh et al. 2018). HepG2 cells treated with fisetin preserve Nrf2 stability and inhibit its degradation (H. Zhang et al. 2019). When tested in aged wild-type rats, or mice with the progeroid syndrome, fisetin was classified as a "potent senolytic agent". Moreover, when administered to wild-type mice late in life, fisetin significantly reduced age-related pathology, restored tissue homeostasis, and extended median and maximum life and health span (Yousefzadeh et al. 2018). It exerts its senolytic effect at doses as low as 5 µg, and no adverse effects have been recorded, even in very high doses (Kirkland et al. 2017).

Quercetin, found in fruits, is similarly salutogenic and approved for use as a clinical senolytic agent. In combination with dasatinib (an anticancer drug), it acts as a confers enhanced senolytic capability (Kirkland et al. 2017). More recently, the effects of long-term treatment with dasatinib plus quercetin in aged mice were tested. The authors concluded that the effects on ageing might be mediated through the modulation of gut microbiota composition. The treatment promoted a reduction in senescent cells (p16 and p21 expression) and inflammation (Cxcl1, IL1-β, IL6, Mcp1 and TNFα expression) in the small and large intestines compared to control mice. It was also verified that the modulation of microbial signatures was more prominent in the small intestine with an increase in the

phylum *Verrucomicrobia* and a lower abundance of the phylum *Firmicutes* in the ileum of treated mice (Saccon et al., 2021). Additionally, quercetin activates SIRT-1, inhibits the NLRP3 inflammasome (L. Alvarenga, Cardozo, Borges, et al. 2020) and the expression of SASP factors and the suppressed IL-Iβ induced activation of the NF-kB pathway cascade (Shao et al. 2021). Quercetin has a therapeutic potential to alleviate endothelial dysfunction in age-related CVD by mitigating endothelial senescence (Dagher et al. 2021). As such, quercetin may be one of most potent anti-inflammatory flavonoids (Martínez, Mijares, and De Sanctis 2019). It has also been recently identified as an anti-viral agent, currently being tested for the ability to treat SARS-CoV-2 (Covid-19) (Williamson and Kerimi 2020).

Other bioactive compounds such as tocopherol, curcumin, berberine, catechin, rutin, and ginkgo Biloba extracts, with senolytic effects, can be obtained from diet, demonstrating the potential of using the concept of food as medicine (Denise Mafra et al. 2021).

Scientific evidence suggests that nutritional intervention involving adequate consumption of a diet rich in compounds with senolytic properties is a prospective strategy to prevent or mitigate the effects of the diseasome of ageing. However, it would be helpful to establish an officially approved daily intake recommended value for polyphenols capable of eliciting a significant senolytic effect (Yousefzadeh et al. 2018) (**Figure 4**).

One of the advantages of using the natural agents and bioactive compounds found in food to prevent senescence is their enhanced safety profile over synthetic agents such as dasatinib, as most naturally occurring senotherapeutic agents have no record of severe adverse effects, even at high doses (Maher 2015). The prototype senolytic agent dasatinib has effects ranging from low white blood cell count, upper and lower respiratory tract infection, anaemia, low blood platelets, rash, diarrhoea, dyspnea and neutropenia (Nekoukar, Moghimi, and Salehifar 2021). In addition, it is important to notice that most studies are performed with only one nutrient. However, people eat food, not nutrients, and here we emphasize that the

food matrix seems crucial to mitigate inflammageing compared to the supplementation with only one nutrient.

The impact of the food on gut microbiota

Foods are also essential to maintaining intestinal mucosal integrity and stable normative gut microbiota (Gebert et al. 2020). High microbial diversity within a stable microbiota is central, as an imbalanced microbiota can elevate the inflammatory burden (**Figure 5**) (Margină et al. 2020).

Fermented foods based on lactic acid bacteria, such as sauerkraut, pickled cabbages, fermented cassava, gundruk, khalpi and kefir, present antioxidant properties. These foods contain *Lactobacillus* and many bioactive compounds which activate Nrf2 expression (D. Mafra et al. 2022). This is again supported by evidence from pre-clinical models, where it has been demonstrated that dietary acquisition of fermented soybeans increased Nrf2 expression, which resulted in both antioxidant and anti-fatigue effects (Cui et al. 2020).

Strategies to revert diseases associated with gut dysbiosis are currently being explored, with the hypothesis that the diseaseome of ageing is tractable to intervention through restoring a normative microbiome (O'Toole and Shiels 2020). Certain therapeutic strategies, including synbiotics, probiotics and prebiotics, have been explored. Although studies on the use of symbiotics as treatment options have been limited, few studies have documented beneficial effects on the gut microbiota in the age-related burden of lifestyle diseases, such as CKD (Cruz-Mora et al. 2014; McFarlane et al. 2019). Probiotics have been reported to improve health in some (Wu et al. 2011) but not in all studies (Borges et al. 2018). A major challenge with this therapeutic approach is that the gut microbiota has an innate ability to resist external influences (Denise Mafra et al. 2021), and their effects can be affected by inter-individual variability and pre-existing health conditions. Studies with prebiotics have demonstrated more consistent results than probiotics (S. P. Singh et al. 2017), acting by

shifting bacterial metabolism towards a saccharolytic fermentation pattern. This has been achieved by a phenomenon called 'cross-feeding', to support intestinal bacteria using excreted products from another strain, resulting in the generation of more beneficial metabolites that benefit both the bacteria and ultimately the host (Graf et al. 2015). Clinical studies have shown that prebiotic supplements positively affect plasma urea levels and uraemic toxins and improve inflammatory status in CKD (Esgalhado et al. 2020).

Macronutrients, including carbohydrates, proteins and fat that are partially absorbed in the ileum, can be processed by the gut microbiota in the colon, providing a greater number of substrates for the growth of gut bacteria (Denise Mafra, Barros, and Fouque 2013).

Another type of food that promotes bacterial growth, though selectively, is foods high in sugars, such as fructose and glucose (Rosas-Villegas et al. 2017). They increase the Firmicutes to Bacteroidetes ratio that has been implicated in higher susceptibility to diseases. They also activate unfavourable physiological processes, such as endotoxemia, overexpression of cytokines (TNF and IL-1β), and toll-like receptor 4 (TLR4) in rat kidneys (Rosas-Villegas et al. 2017). As endotoxemia contributes to inflammation and metabolic disorders, gut dysbiosis could be a suitable explanation for the association between high sugar consumption and increased incidence of certain age-related diseases, such as CVD and CKD. In the case of dietary proteins, their digestion and absorption occur partly in the ileum (Scott et al. 2013). Their fermentation which occurs in the colon by the action of proteolytic bacteria results in the generation of both beneficial compounds (e.g., SCFAs and polyphenols) and toxic end products (e.g., amines, phenols and thiols) (Denise Mafra, Barros, and Fouque 2013). Significantly, cooking methods, general food processing methods and protein sources are essential determinants of the outcome of microbial metabolism of proteins (Nyangale, Mottram, and Gibson 2012; Madsen et al. 2017).

High-fat diets, for example, reduce total microbiota content in faeces, and increase endotoxemia and intestinal permeability (Wisniewski, Dowden, and Campbell 2019). Decreased SCFAs and elevated circulatory concentration of pro-inflammatory markers have also been reported in healthy young adults consuming a high-fat diet compared to the lower-fat diet group (Wan et al. 2019). Additionally, fish oil, a rich source of omega 3 polyunsaturated fatty acid, restores intestinal barrier function and trans fatty acid, abundantly present in processed food such as pastries, fried potatoes, snacks, and margarine, promotes microbial dysbiosis and poor health (Ge et al. 2019). It is important to note that omega-3-rich foods have been recorded with a greater beneficial impact on the gut microbiome than omega-3 supplements (Costantini et al. 2017), emphasising the importance of a holistic food-based approach over a nutrient-based approach.

The consumption of plant-based polyphenolic compounds has also been associated with the modulation of gut microbiota. Due to their low bioavailability, the majority of the dietary polyphenols enter the circulation through the colon and could modulate the composition and function of the gut microbiota (Ozdal et al. 2016). In a study involving blueberry supplementation in a murine model, beneficial changes were observed in the gut microbiota, characterised by increased prevalence of Bifidobacterium and Lactobacilli, which mitigated inflammageing and improved inflammation insulin signalling (S. Lee et al. 2018).

Generally, human diets are highly varied and have complex effects on the gut microbiota. However, some diets are more salutogenic than others. For example, the Mediterranean diet promotes the growth of saccharolytic microbial species. In contrast, the Western diet, characterised by a high intake of red meat, refined grains, and ultra-unprocessed foods, resulting in high sugar, salt, animal protein and saturated and hydrogenated fats, enables dysbiosis (Garcia-Mantrana et al. 2018). A Western diet supports decreased saccharolytic and increased proteolytic bacterial growth typical of many age-related diseases (Bischoff

2016). Thus, a balanced gut ecosystem may reduce the risk of age-related disease development by reducing the risk of unfavourable physiological processes, such as endotoxemia and inflammation. Few studies have investigated the effects of a wide range of dietary patterns on the gut microbiota in humans and the effect of external factors. However, through advances in biostatistics and metagenomics, personalised dietary therapy that targets the gut microbiota in disease prevention is promising, solidly placing the food as medicine approach as a key player in the achievement of prolonged healthspan.

Conclusion

Emerging data has revealed a significant role of food in mitigating aspects of ageing-related disease. In particular, it has been demonstrated to combat inflammageing associated with many chronic burdens of lifestyle diseases. Targeting the foodome using "Food as Medicine" may be an attractive way to restore a normative gut microbiome and thus mitigate the effects of their metabolites. Nutrients that can assist in modulating inflammatory processes by regulating transcription factor activity, such as reducing activation of NF-kB and NLRP3 and increasing Nrf2 expression and activity, are also key to such an approach. However, the adoption of Food as Medicine should be based on robust scientific evidence gleaned from carefully designed clinical trials. Thus, carefully choosing the foods and trialling them may help us to increase healthspan - "*The power is on your plate*".

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- Conflict of interest:

P.S. is on the scientific advisory boards of REATA, AZ, Baxter Healthcare and Vifor.

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Figure 1. Pictorial representation of biological mechanisms involved cellular senescence, resulting in the exacerbation of the inflammatory phenotype. Cellular senescence is a key feature of ageing, and it is initiated by several stimuli, such as endogenous and exogenous sources of reactive oxygen species (ROS) such as ionising and UV radiation, environmental toxins), oncogenic and genotoxic chemicals and heat shock, which mediates cellular and organ damage during ageing. These mechanisms activate $p16^{ink4a}$ and $p14^{ARF}$, p38, p53, MAPK, nuclear factor-κB (NF-κB). Senescence is also characterised by low grade sterile chronic inflammation (termed 'inflammageing') due to a senescence-associated secretory phenotype (SASP), which contributes to the overall inflammatory burden. Created with Biorender.

Figure 2. A pictorial overview of the beneficial effect of the relationship between gut microbiota and inflammageing. Ageing is related to reduced microbial diversity, with the increased gut composition of pathobionts, increasing microbiota-derived metabolites such as indole-3-acetic acid (IAA), p-cresyl sulfate (PCS), indoxyl sulfate (IS), phenylacetylglutamine (PAG), trimethylamine N-oxide (TMAO) and lipopolysaccharides (LPS), and reduction of short-chain fatty acid (SCFA) production and intestinal alkaline phosphatase (IAP), which are associated with NF-kB activation, leading to inflammageing. Image created with Biorender.

Figure 3: Effect of an epigenetic modulating diet on epigenome maintenance. Diet influences the methylome via the provision of methyl groups to cells, thus modulating the methylation status of the epigenetic landscape. Methyl donors are major constituents of the epigenetic diet.

Figure 4. Mechanisms involved in the modulation of cellular senescence by nutritional components. Most age-related diseases involve an interplay between several factors such as increased ROS production and DNA damage that results in the resistance of cellular senescence. Such cells are resistant to apoptosis and possess a pro-inflammatory SAS. Many bioactive compounds found in vegetables and fruits can combat this by mitigating inflammation, and increasing the expression of Nrf2, HO1 and SIRT1. These compounds can also decrease the expression of PYD domains-containing protein 3 (NLRP3) inflammasome, nuclear factor-κB (NF-κB), mammalian target of rapamycin (mTOR), Mitogen-activated protein kinase (MAPK), Inhibitory-κB Kinase (IKKα), nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IKBα).

Figure 5. Food as Medicine. Food intake modulates health span by mediating changes in gut microbiota and inflammageing.