

Review

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Posted Date: 9 April 2025

doi: 10.20944/preprints202504.0821.v1

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Review

The Role of Nutraceuticals and Functional Foods in Mitigating Cellular Senescence and Its Related Aspects: A Key Strategy for Delaying or Preventing Aging and Neurodegenerative Disorders

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Abstract: As life expectancy continues to increase, it becomes increasingly important to extend healthspan by targeting mechanisms associated with aging. Cellular senescence is recognized as a significant contributor to aging and neurodegenerative disorders. This review examines the emerging role of nutraceuticals and functional foods as potential modulators of cellular senescence, which may, in turn, influence the development of neurodegenerative diseases. An analysis of both epidemiological and experimental studies indicates that bioactive compounds, including polyphenols, vitamins, and spices, possess substantial antioxidants, anti-inflammatory, and epigenetic properties. These nutritional senotherapeutic agents effectively scavenge reactive oxygen species, modulate gene expression, and decrease the secretion of senescence-associated secretory phenotype factors, minimizing cellular damage. Nutraceuticals can enhance mitochondrial function, reduce oxidative stress, and regulate inflammation, key factors in aging and diseases like Alzheimer's and Parkinson's. Furthermore, studies reveal that specific bioactive compounds can reduce senescence markers in cellular models, while others exhibit senostatic and senolytic properties, both directly and indirectly. Diets enriched with these nutraceuticals, such as the Mediterranean diet, have been correlated with improved brain health and the deceleration of aging. Despite these promising outcomes, direct evidence linking these compounds to reducing senescent cell numbers remains limited, highlighting the necessity for further inquiry. This review presents compelling arguments for the potential of nutraceuticals and functional foods to promote longevity and counteract neurodegeneration by exploring their molecular mechanisms. The emerging relationship between dietary bioactives and cellular senescence sets the stage for future research to develop effective preventive and therapeutic strategies for age-related diseases.

Keywords: cellular senescence; *inflammaging*; healthy aging; neurodegenerative diseases; nutraceuticals; functional foods; Alzheimer's disease; Parkinson's disease

1. Introduction and Background

Life expectancy has dramatically increased in nearly all nations, and the global population has tripled since the mid-twentieth century. By 2030, the global human population is projected to grow to approximately 8.5 billion, with an additional 1.18 billion people expected in the following two decades, reaching 9.7 billion in 2050 [1]. Aging is rapidly accelerating worldwide. By 2050, the number of people over 65 is expected to more than double, reaching 1.5 billion, representing 16% of the global population. While this trend is more intense in developed countries - where 26% of the European and North American population are over 65 - it has also become a significant global phenomenon that affects developing countries [2,3]. Nevertheless, insufficient evidence suggests that an increase in longevity correlates with a more extended period of good health [4]. Indeed, a notable

difference exists between lifespan, defined as the total years lived, and healthspan, which refers to the duration without disease [5]. Extending lifespan without postponing the onset of diseases or lessening their severity would worsen the healthspan-lifespan gap. Advanced age is marked by the emergence of various complex health conditions, such as age-related diseases (ARDs) and geriatric syndromes (GSs), also referred to as “chronic or non-communicable” diseases, that are the leading cause of mortality and disability worldwide [6].

Aging is an inescapable, natural and universal feature of most living organisms that results from environmental, genetic, epigenetic and stochastic factors, each contributing to the overall phenotype [7,8]. As humans age, damaging changes accumulate in the molecules, cells, and tissues, leading to a decline in normal physiological functions and a reduced ability to maintain adequate homeostasis. The increased susceptibility to various stressors and reduced ability to adapt to the environment lead to clinical diseases, where genetic, epigenetic and environmental factors play a key role [9]. Geroscience provides a new perspective on gerontology by investigating the link between aging and ARDs. Both epidemiological evidence and experimental research demonstrate that aging is the principal risk factor for ARDs and GSs. Geroscience posits that aging and ARDs/GSs share a fundamental set of biological mechanisms, and twelve biological processes have been identified as the critical pillars of aging and ARDs (Figure 1).

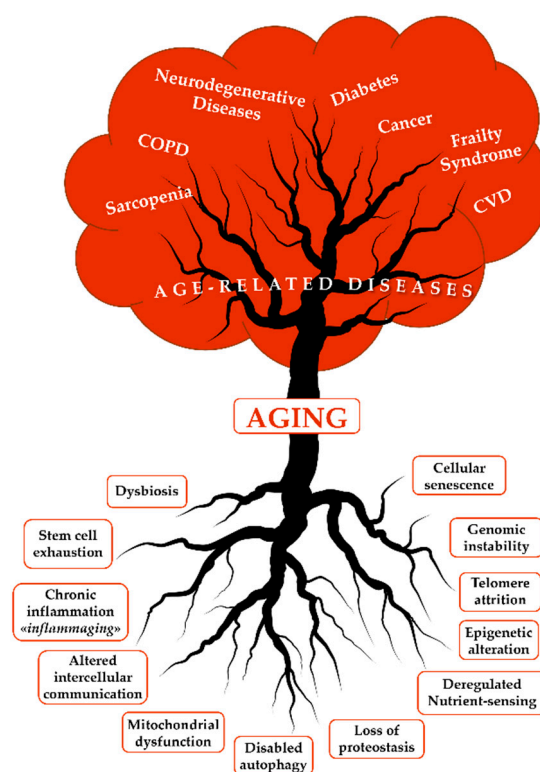


Figure 1. The Hallmarks of aging. Aging is a multifactorial process at various levels, from molecules to cells, organs to systems, ultimately affecting the entire organism. In 2023, López-Otín and colleagues refined the framework of aging hallmarks, identifying 12 key features: dysbiosis, stem cell exhaustion, chronic inflammation (*inflammaging*), altered intercellular communication, mitochondrial dysfunction, epigenetic alterations, impaired macroautophagy, loss of proteostasis, deregulated nutrient sensing, telomere attrition, genomic instability, and cellular senescence.

These hallmarks are intricately linked and interconnected and represent the fundamental changes associated with aging (the roots of aging). As aging advances, it broadly supports the onset of ARDs, including chronic obstructive pulmonary disease (COPD), sarcopenia, diabetes, cancer, frailty syndrome, cardiovascular diseases (CVDs), and neurodegenerative disorders like Alzheimer’s

and Parkinson's diseases. Just as a tree derives nourishment from its roots, these health issues represent the fundamental biological alterations of aging.

The hallmarks of aging appear to be closely interconnected, forming a finely controlled network in which cellular senescence and inflammation represent the "umbrella" that encompasses all these mechanisms [10,11].

In common, all hallmarks are time-dependent on the aging process and can be manipulated by laboratory experiments to accelerate or by therapeutic interventions to slow down the aging process [12]. Therefore, medicine's primary objective should be to tackle the aging process and enhance the mechanisms that can prevent, delay, or counteract ARDs/GSs [13,14]. An integrated hypothesis proposes that ARDs/GSs manifest an accelerated aging process, indicating that the aging phenotype and ARDs/GSs are not distinct entities but the outcomes of the same common set of molecular and cellular processes, likely occurring at varying rates [15]. Which are the determinants that make the aging trajectories more or less steep? Environmental conditions, such as the intensity and types of stressors and lifestyle, are important health factors. However, the body's ability to respond to and adapt to these stressors is even more crucial. This capacity is influenced at least partly by an individual's genetic background and epigenetic changes, which play a significant role in various adaptation and remodeling processes.

Hormesis is a potential mechanism that explains the relationship between healthy aging and the development of ARDs/GSs. Lifelong low-intensity stressors activate maintenance and repair mechanisms that positively affect health. However, increasing the intensity of these stressors can surpass the ability of organs and systems to adapt, resulting in detrimental effects. The emerging concept defines aging as malleable. By targeting the hallmarks of biological aging, such as cell senescence and its interdependent features, it is possible to alleviate ARDs and dysfunctions, thereby extending longevity. Additionally, using external molecules to boost the body's natural cellular defense mechanisms is proposed as a promising anti-aging strategy centered on hormetic-based protection [16].

A recent multi-omics data study has shown that different organs and tissues can age at distinct rates within the same individual [17]. Brain pathologies and changes in brain structure are commonly seen in aging [18], with significant modifications in the brain's intricate microstructure resulting in cognitive decline [19]. Brain morphology evolves with age and most commonly undergoes significant atrophy [20]. These changes are flanked, if not directly the cause, by cognitive deficits that include memory loss [21,22], reduced motor performance [23], and behavior [24].

Among neurodegenerative diseases, Parkinson's disease (PD) and Alzheimer's disease (AD) are the most common. Usually, they have a late debut of the manifestation with a subsequent stage of progression leading to signs of dementia with similar symptoms, such as memory impairment, orientation problems, and difficulties in performing service functions. In central nervous system (CNS) health, the brain aging trajectory is closely linked to cellular damage accumulation and the onset of neurodegenerative processes. An emerging pivotal factor contributing to the decline of brain structure and function is cellular senescence, a state of stable growth arrest, macromolecular damage, and altered metabolism associated with a hypersecretory and pro-inflammatory phenotype known as the senescence-associated secretory phenotype (SASP). Neuroinflammation may be one of the factors responsible for the increased cognitive decline and risk of AD and PD [25].

This article comprehensively reviews recent advancements concerning the impact of various nutraceuticals and foods on cellular senescence. It delves into key factors associated with this process, such as inflammation, macromolecular damage, mitochondrial dysfunction, and oxidative stress. These factors are critical as they represent common pathways linked to aging and neuronal damage. The review highlights how these dietary components may influence the above-mentioned mechanisms, potentially offering therapeutic avenues to mitigate the effects of aging at the cellular level.

2. The Role of Senescence in Aging and Neurodegenerative Diseases

Senescence is considered a highly dynamic, multi-step process over which the properties of senescent cells continuously evolve and diversify context-dependently [26]. Formally described in 1961 by Hayflick and colleagues, cellular senescence was initially observed in normal human fibroblasts that stopped proliferating after a finite number of divisions [27]. Subsequent studies have proven that a variety of stressors, including oxidative stress, DNA damage, oncogene activation, mitochondria deterioration, chemotherapy and exposition of ionizing radiations, can trigger a “stress-induced premature senescence” in vitro [28,29].

Senescence activation leads to several molecular changes and distinct phenotypic alterations, including chromatin remodeling, shortened telomeres, accumulation of DNA damage and reactive oxygen species (ROS), activation of cell cycle inhibitory pathways, lysosome enlargement, macromolecular disruption, metabolic disbalance, apoptosis resistance and SASP [30]. SASP is characterized by synthesizing various biologically active molecules, such as inflammatory mediators, growth factors and extracellular matrix proteins. These factors reinforce the senescent phenotype through autocrine or paracrine signaling and can also affect the microenvironment, influencing neighboring cells and distant locations within the organism [29] (Figure 2).

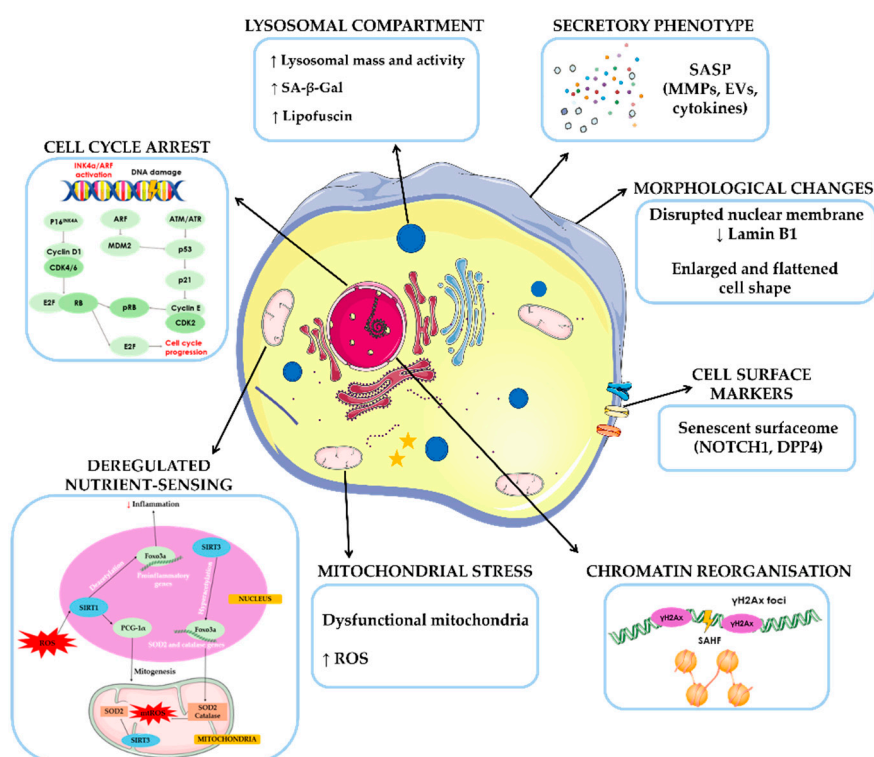


Figure 2. The Hallmarks of cellular senescence. Senescent cells undergo distinct morphological and molecular alterations defining cellular senescence's hallmarks. At the genomic level, senescence is characterized by stable cell cycle arrest, primarily driven by the p16^{INK4a}/Rb and p21^{CIP1}/p53 pathways. Chromatin reorganization is a key feature, marked by senescence-associated heterochromatic foci (SAHFs) and γ -H2AX foci, indicating DNA damage. Lysosomal alterations are also evident, with increased lysosomal mass and activity, elevated expression of senescence-associated β -galactosidase (SA- β -Gal), and lipofuscin accumulation. Senescent cells exhibit notable morphological changes, including enlargement, flattening, and modifications in membrane structure. A feature of nuclear dysfunction is the downregulation of Lamin B1, leading to nuclear envelope instability. The senescent surfaceome is enriched with specific channels and receptors, such as NOTCH1, DPP4, and B2M. Mitochondrial dysfunction is another critical feature, leading to increased ROS production and deregulated nutrient sensing. SIRT1 and SIRT3 play pivotal roles in mitochondrial homeostasis and oxidative stress regulation. SIRT1, located in the nucleus, modulates mitochondrial function by deacetylating FOXO3a, reducing inflammatory protein expression, and activating PGC-1 α to promote mitochondrial biogenesis. Oxidative stress

inactivates SIRT3, leading to SOD2 hyperacetylation and increased mitochondrial ROS (mtROS), creating a vicious cycle of oxidative stress and mitochondrial dysfunction. SIRT3-mediated deacetylation of FOXO3a and SOD2 counteracts ROS accumulation by upregulating antioxidant defenses, including catalase. Finally, a defining feature of senescence is the SASP, characterized by the secretion of pro-inflammatory cytokines (e.g., IL-1 β , IL-6, TNF- α , etc.) and matrix metalloproteinases (MMPs), often encapsulated in extracellular vesicles (EVs). \uparrow increase; \downarrow decrease.

As the number of senescent cells increases with age, there is increasing evidence suggesting their involvement in the pathogenesis of ARDs [31–33], including neurodegenerative diseases such as AD and PD [34]. Moreover, PD and AD are called “protein misfolding diseases” because deposits of improperly folded and modified proteins are detected in specific areas of the patient’s brain, leading to neuronal damage [35]. It has been reported that the final dysfunction and neuronal loss observed in neurodegenerative diseases are often flanked by malfunctions of other types of CNS cells, such as microglia and astrocytes. Various types of cells in the nervous system have been identified as undergoing the senescence process, including neural stem cells, neurons, astrocytes, oligodendrocytes and microglia. In a state of senescence, microglia are neurotoxic and become detrimental in many neurodegenerative diseases by producing inflammatory cytokines, superoxide anions, and nitric oxide, promoting the phenomenon of ‘*oxi-inflamm-aging*’, which contributes to the neuropathogenesis [36–38].

Evidence shows that senescent astrocytes accumulate in AD and PD patients, promoting inflammation through the SASP factors [39–41]. Indeed, several SASP factors, including MMP-3, IL-1 α , IL-6, and IL-8, are increased in PD and AD brain, indicating that cellular senescence could contribute to neurodegeneration [42–44]. In addition, in the brain tissue of PD patients, α -synuclein deposition correlates with increased senescent cell accumulation and higher SA- β -Gal expression, suggesting the role of cellular senescence in the pathogenesis of PD [45]. Conversely, attenuation or elimination of cellular senescence has been shown to alleviate neuroinflammation in AD and PD models [43,46]. Moreover, a recent study revealed that senescent neurons with tau neuropathology are prevalent in patients with AD [47], while the removal of accumulated senescent glial cells attenuated cognitive decline and age-related neurodegenerative disorders [48].

Therefore, eliminating senescent cells within the CNS, or at least delaying their senescence, and mitigating the adverse effects of a spreading SASP have been identified as targets for the prophylaxis and adjunctive treatment of neurodegenerative diseases.

Furthermore, the SASP can be viewed as an ‘inflammatory chain reaction’ that promotes damaging effects and contributes to systemic *inflammaging*; thus, biomolecules with antioxidants and anti-inflammatory properties would be beneficial not only as protectors against senescence induction but also as tools to extinguish the inflammatory ripple effect [38].

3. Nutritional Interventions to Slow Down Aging

The hallmarks of aging constitute an interconnected network of fundamental mechanisms that influence aging and can be modulated by lifestyle factors, including nutrition, to improve human healthspan [49]. Aging is a malleable process characterized by an intra- and inter-individual heterogeneous and dynamic balance between accumulating damage and repair mechanisms. Nutritional interventions that help slow this process can reduce cellular damage and accumulation of senescent cells or enhance the ability of cells, tissues, or the organism to repair or adapt to that damage [50]. In this context, several natural compounds, known as “bioactive compounds,” can interact with biological processes, and when present in food, they are referred to as “nutraceuticals” [51]. As discussed in the next paragraph, many studies focus on identifying bioactive compounds with preventive effects against pathological conditions or with broader anti-aging properties. Moreover, emerging evidence suggests that dietary factors can influence brain health and cognitive function, providing a promising avenue for intervention [52].

In this context, it is also important to highlight that some nutraceuticals may exhibit hormetic behavior, displaying a biphasic dose-response relationship in which low doses provide beneficial effects, whereas high doses may be detrimental. These positive effects at low concentrations arise from stimulating adaptive stress responses, ultimately enhancing the body's resilience to various stressors. This phenomenon is particularly evident among polyphenols, such as curcumin and resveratrol [53].

Recently, the focus has been on identifying nutraceuticals that mimic metformin and rapamycin without their collateral effects. Among these, researchers have individuated withaferin A, allantoin, ginsenoside, and epigallocatechin gallate as promising candidates for experimental validation [54,55]. They showed strong activation of the cAMP pathway, which was recently found to induce anti-aging effects similar to caloric restriction (CR) via up-regulation of sirtuins (SIRT1 and SIRT3) [56]. SIRT1 and SIRT3, particularly SIRT1 and SIRT3, are key regulators of cellular metabolism, stress responses, and aging. As NAD⁺-dependent deacetylases, they are activated under CR, promoting longevity and healthspan by modulating energy metabolism, mitochondrial function, and stress resistance. SIRT1 acts as a nutrient sensor, regulating epigenetic modifications, mitochondrial quality, and anti-inflammatory responses, while SIRT3 enhances mitochondrial protein deacetylation, optimizing oxidative metabolism and aerobic fitness, both contributing to the lifespan-extending effects of CR [57–59].

CR consists of a 25–50% calorie reduction compared to a standard diet, with preservation of the vitamins and minerals supply [60]. In addition to SIRT1 and SIRT3, CR modulates other key nutrient signaling pathways, including insulin/IGF-1, mTOR, and AMPK, leading to a reduction in oxidative stress, enhancement of mitochondrial function, activation of anti-inflammatory responses, stimulation of neurogenesis, and increased synaptic plasticity, emphasizing the positive impact of CR on brain functions. These effects can delay cellular senescence and may significantly mitigate age-related functional decline [61]. Experimental studies have reported that CR reduces molecular features of cellular senescence in different models [62–64]. Interestingly, a recent study demonstrated that moderate CR could decrease circulating biomarkers of cellular senescence in healthy young to middle-aged humans without obesity, highlighting the impact of lifestyle [65]. Moreover, dietary restriction and plant-based dietary patterns have been linked to improved key clinical outcomes associated with aging, especially body composition changes, lipid profile, blood pressure, lipid peroxidation, inflammation, and cardiometabolic risk [66–73]. Despite the mechanisms not being fully elucidated, these benefits suggest that such dietary approaches may be crucial in promoting healthy aging by modulating metabolic and inflammatory pathways central to age-related physiological changes and disease prevention. However, in CR, the timing of initiation is a critical factor; when started at an early age, it is associated with beneficial effects [74]. Conversely, in older adults, CR may exacerbate sarcopenia and osteopenia, contributing to muscle and bone loss [75].

In addition to CR, other dietary patterns have been proposed to promote healthy aging. Among these, the Mediterranean diet (MedDiet) is the most studied. MedDiet is characterized by a high intake of vegetables, fruits, whole grains, and fish, and it has demonstrated significant health benefits, including the prevention of ARDs. Its protective effects are mainly attributed to its rich composition of bioactive compounds that help modulate oxidative stress, inflammation, and metabolic processes, further supporting its role in longevity and overall well-being [76–80] and reducing cognitive impairment [81]. Intriguingly, emerging proofs suggest that adherence to the MedDiet may contribute to delaying cellular senescence [82]. In older adults, adherence to MedDiet has been associated with a lower proportion of endothelial cells with shorter telomeres, an effect likely mediated by decreased ROS production and apoptosis [83]. Furthermore, Mantilla-Escalante suggests that long-term adherence (1 year) to the MedDiet, particularly when enriched with nuts, can modulate the expression of several microRNAs (miRNAs) involved in cellular senescence, including cell cycle regulators and pro-inflammatory markers. MedDiet, through miRNA-mediated gene modulation, may influence fundamental mechanisms of aging and cellular homeostasis [84].

Even if the mechanisms through which food influences aging are not fully understood, several bioactive compounds have been reported to function as epigenetic modulators, influencing gene

expression, chromatin organization, DNA methylation patterns, and non-coding RNA expression [85,86]. Interestingly, the human epigenome is influenced by exogenous factors such as nutrition, a field explored in nutritional genomics. Both the quality and quantity of diet have been found to modulate DNA methylation and mental health epigenetically [87].

Additionally, an intriguing hypothesis suggests that bioactive compounds in food may extend healthspan by modulating SASP, indicating new strategies to slow the onset and progression of ARDs [88]. Since the anti-aging effects of natural compounds have only recently begun to be scientifically evaluated, very few notions are available about their properties and ability to exert anti-SASP and/or senolytic activity. However, nutrition is often considered one of the most promising modifiable risk factors for ARDs, including neurodegenerative diseases, a contention fully appreciated in multidomain intervention studies [89–91].

While all-natural foods are inherently functional due to their composition, the concept of functional foods emerged from the observation that certain manufactured foods, enhanced with additional ingredients, can further improve human health [92]. This category includes conventional foods enriched with bioactive compounds such as vitamins, minerals, and phytochemicals [94,95], directly impacting nutritional health by enhancing overall well-being or reducing disease risk [93]. Among the various nutraceutical-enriched foods, olive oil, milk, and yoghurt stand out for their potential health benefits. Extra virgin olive oil has been extensively studied for its positive effects on telomere length, diabetes, cognitive function, and various hallmarks of aging, including cellular senescence [94]. Similarly, the impact of fortified milk on inflammaging parameters has been investigated by Martucci et al. in 2020. The fortified milk was enriched with omega-3 fatty acids (EPA, DHA), various vitamins, and trace elements, finding improved levels of micronutrients and the omega-3 index, along with reduced arachidonic acid (AA), homocysteine and omega-6/omega-3 ratio [95]. Yoghurt, rich in anti-inflammatory and B-vitamin content, may help protect against cognitive decline, as shown by Tillisch et al., who reported brain function changes linked to fermented dairy intake [96].

Functional foods play a crucial role in healthy aging by addressing factors like oxidative stress, inflammation, and mitochondrial dysfunction. Their positive effects on aging mechanisms suggest potential benefits for aged people [97]. By modulating many biological mechanisms in mammalian body and cells, it could be proposed the following anti-aging mechanisms of functional foods: i) Stabilizers of mitochondrial membranes and enhancers of mitochondrial function, agents that avoid cell death by apoptosis or necrosis, ii) Metal chelating activities, iii) Antioxidants, iv) Inducers of apoptosis of preneoplastic and neoplastic cells [98–101].

The distinction between nutraceuticals and functional foods is often blurred due to their intrinsic overlap, as nutraceuticals represent a specific subset of functional foods. Given this complexity, our review will specifically focus on nutraceuticals to provide a more structured and comprehensive analysis of their role in neurodegenerative diseases, specifically AD and PD. By narrowing our scope, we aim to offer a clearer perspective on their mechanisms of action and potential therapeutic applications.

4. Nutraceutical Interventions in Neurodegenerative Disorders: Focus on Parkinson's and Alzheimer's Diseases

The aging brain is highly susceptible to neurodegenerative diseases, but the exact mechanisms through which senescence in the CNS contributes to neuropathogenesis remain unclear. The number of senescent cells increases with age, and there is growing evidence suggesting the involvement of cellular senescence in the neuropathogenesis of AD and PD, resulting in a significant increase in chronic neuroinflammation due to the SASP. Therefore, countering and removing senescent cells in the brain, or at least postponing their senescence and alleviating the adverse effects of spreading SASP, could be a strategy for helping to slow the progression of AD and PD or delaying their onset.

This paragraph reviews studies investigating nutraceutical compounds that may mitigate cellular senescence processes in the brain, including neuroinflammation and the reduced expression

of anti-apoptotic proteins such as Bcl-2 and Bcl-xl, as well as demonstrating senostatic and senolytic effects. Although direct evidence linking nutraceuticals to cellular senescence in neurodegenerative diseases is currently limited, this field has considerable potential. Various nutraceuticals have shown beneficial effects across numerous models by modulating traits associated with senescence, indicating that further research may provide valuable insights into their advantages.

Given the established role of senescent cells in neurodegenerative diseases, we suggest that nutraceutical compounds affecting senescence-associated features may yield beneficial outcomes in these conditions. However, due to the lack of direct evidence, our discussion will primarily focus on key molecular and cellular mechanisms related to senescence rather than directly indicating their effects on senescent cells in neurodegeneration.

The compounds discussed are categorized based on their natural origins.

4.1. Antioxidant Vitamins

A major contributor to aging and ARDs, such as AD [102] and PD [103] is oxidative stress induced by free radicals. ROS, natural byproducts of cellular metabolism increased in senescent cells, play dual roles in biological systems. At low to moderate concentrations, ROS support essential physiological processes; however, when their levels become excessive, oxidative stress ensues, leading to damage to critical cellular components, including lipids, proteins, and DNA and also can induce cell senescence [104–106]. This oxidative stress can directly activate glial cells, mainly by priming astrocytes, resulting in their interaction with neurons and subsequent release of immune mediators such as nitric oxide (NO), additional ROS, pro-inflammatory cytokines, and chemokines. These mediators act as neurotoxins, propagating inflammation within the CNS [107].

Accumulating evidence from mouse models of accelerated senescence indicates that ascorbic acid (AAC) plays a rescuing role in premature aging. Moreover, although the precise role of AAC in the CNS remains only partially understood, studies have demonstrated that its concentration in the cerebrospinal fluid (200–400 mM) far exceeds that found in cerebral parenchyma and plasma (30–60 nM) [108]. Overall, AAC exhibits notable nootropic properties [109] and has been shown to decrease acetylcholinesterase activity in mice [110]. In addition, it facilitates the differentiation of neuronal and astrocyte precursors, thereby promoting synaptic maturation [111]. AAC is also essential for the biosynthesis of catecholamines, peptide amination, myelin formation, and enhancement of synaptic function while providing neuroprotection against glutamate toxicity [112,113].

In PD, dopamine metabolism generates oxidative stress products that contribute to accumulating abnormal proteins that are characteristic of PD [114]. Current therapeutic strategies for PD primarily alleviate symptoms, but they do not halt disease progression, rendering treatment particularly challenging.

Although early studies indicated that AAC supplementation could mitigate oxidative damage in vitro and animal models [115,116], more recent investigations have yielded inconsistent results [117]. Notably, AAC levels are lower in the substantia nigra compared to other brain regions [118,119], heightening its vulnerability to oxidative stress [120]. Furthermore, AAC has been shown to enhance the production of dihydroxyphenylalanine (DOPA); Seitz et al. observed a dose-dependent overproduction of DOPA in the human neuroblastoma cell line SK-N-SH following incubation with AAC (100–500 mM) for 2 hours [121]. Nonetheless, AAC has been demonstrated to improve the absorption of levodopa in elderly PD patients with poor levodopa bioavailability, thereby enhancing its therapeutic efficacy and reducing its side effects [122,123].

Moreover, AAC is critical for brain development; one study reported that AAC treatment induced a tenfold increase in dopaminergic differentiation in CNS precursor cells derived from the E12 rat mesencephalon [124]. In vivo, a cohort study of 1,036 PD patients further supported the neuroprotective role of AAC, demonstrating that higher dietary intake was significantly associated with a reduced risk of PD [125], although some studies have not corroborated these findings [126,127].

In contrast, the neuroprotective effects of vitamin E are thought to arise from its ability to prevent oxidative stress and inhibit apoptosis. Vitamin E has been shown to reverse impaired synaptic plasticity in mouse models [128] and reduce ROS levels in *Drosophila* models [129]. Additional evidence underscoring the role of oxidative stress in PD includes observations that cellular antioxidants such as glutathione (GSH) are depleted in PD [130] and that treatment with antioxidants, including vitamin E, can protect mice and cultured cells from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity [131].

Specific isoforms of vitamin E, such as γ -tocotrienol and δ -tocotrienol, exert neuroprotective effects through the ER β -PI3K/Akt signaling pathways in SH-SY5Y cells [132]. Moreover, δ -tocotrienol has been found to prevent dopaminergic neuron loss and improve motor function in mouse models of PD; its neuroprotective effect, however, was attenuated by ER inhibitors [133]. In an MPTP-induced PD model in C57/B1 mice, vitamin E-deficient animals were markedly more susceptible to MPTP toxicity, exhibiting increased lethality and greater depletion of dopamine metabolites in the substantia nigra [134]. Perry et al. [135] similarly reported that mice pretreated with daily subcutaneous injections of high-dose α -tocopherol (α T) (2350 mg/kg body weight) for 48 hours before and 72 hours after MPTP administration experienced partial protection against the loss of striatal dopamine and dopaminergic neurons in the substantia nigra. In supporting these experimental findings, a cross-sectional study involving participants over 40 years of age found that higher vitamin E intake was significantly associated with a reduced risk of PD [136].

Conversely, L-AAC has also garnered attention for its beneficial effects on AD [137]. The primary neuroprotective mechanisms attributed to AAC include ROS-scavenging activity, neuroinflammation modulation, A β fibrillation inhibition, and chelation of metals such as iron, copper, and zinc [138]. Furthermore, AAC has been shown to protect SH-SY5Y neuroblastoma cells from A β -mediated apoptosis [139] and, when administered orally, to reduce oxidative stress and neuroinflammation induced by A β fibrils in rats [140].

In contrast, vitamin E is a potent antioxidant that scavenges free radicals primarily through a hydrogen atom transfer mechanism. This reaction yields a non-radical product and a vitamin E radical, which can subsequently react with another radical to form a stable compound, interact with lipids, or be regenerated by reducing agents such as AAC or ubiquinol [141]. Vitamin E plays a crucial role in the brain, is one of the most potent antioxidants, and has shown significant benefits in AD [142]. It counteracts A β -induced oxidative stress [143]; for instance, vitamin E has been demonstrated to prevent A β ₁₋₄₂-induced protein oxidation, ROS production, and neurotoxicity in primary rat embryonic hippocampal neuronal cultures [144]. Moreover, although A β ₁₋₄₂ reduces the surface expression of the principal glutamate transporter, GLT-1, in adult mouse astrocytes, this detrimental effect is prevented by a water-soluble analogue of vitamin E [145]. Vitamin E also helps preserve calcium homeostasis, protects against damage from A β deposits near cell membranes [146], and prevents oxidative stress-induced Tau hyperphosphorylation [147,148]. Additionally, it can inhibit neuroinflammation by suppressing the production of prostaglandins E₂ and D₂, along with reducing cyclooxygenase and lipoxygenase activity [149,150].

Limited evidence directly links the triad of cellular senescence, neurodegenerative diseases, and antioxidant vitamins. Most studies have focused on other cell types, with only a few providing insight into their potential role in modulating senescence-related pathways. To offer a broader perspective, we highlight some relevant findings. For instance, Jeong et al. reported that AAC significantly reduced SA- β -Gal activity by suppressing cell-cycle inhibitors (p53, p21, p16, and pRb) while stimulating cell-cycle activators (E2F1 and E2F2). This finding demonstrated its ability to prevent cellular senescence in vitro and in vivo using human dermal fibroblasts and hairless mice models [151]. Similarly, another study showed that co-incubation with AAC significantly downregulated SA- β -Gal staining, reduced senescence-associated gene expression, and improved cell migration, mineralized nodule formation, and the expression of dentine sialophosphoprotein (DSPP) and bone sialoprotein (BSP) genes in LPS-treated human apical papilla cells [152]. Limited studies are also available regarding vitamin E supplementation. In particular, vitamin E has been shown to reduce

the number of SA- β -Gal positive cells in vitro in human umbilical vein endothelial cells and human fibroblasts [153]. One study revealed that vitamin E ability to decrease SA- β -Gal activity in human fibroblasts depends on the donor's age and cell passage number.

Specifically, while vitamin E reduces SA- β -Gal levels in cells from both young and aged donors at replicative senescence in fibroblasts from older subjects, this effect occurs even at earlier passages. This may be attributed to the phosphorylated form of vitamin E, α -tocopheryl phosphate (α TP), which accumulates with aging due to a reduced conversion to α T. Notably, α TP is more effective than α T in decreasing CD36 expression and CD36-mediated senescence [154].

To conclude, AAC exerts neuroprotective effects by scavenging ROS, modulating neuroinflammation, and supporting synaptic function, while vitamin E mitigates oxidative stress, preserves membrane integrity, and inhibits apoptosis. Although studies indicate potential positive outcomes on senescence-associated characteristics, findings remain inconsistent in AD and PD, highlighting the need for further research to elucidate their precise mechanisms and therapeutic potential.

4.2. Polyphenols

Dietary polyphenols exhibit robust neuroprotective effects that extend well beyond their well-known antioxidant and anti-inflammatory properties. Circumstantial evidence indicates that these compounds modulate intracellular signaling pathways, alter gene expression, and influence enzyme activities, all contributing to their therapeutic potential in neurodegenerative diseases [155,156].

A growing body of research demonstrates that polyphenols can modulate cellular senescence. For example, chronic treatment of pre-senescent neonatal human dermal fibroblasts with oleuropein aglycone, a prominent polyphenol in extra-virgin olive oil, resulted in a significant reduction in senescent cell numbers, as evidenced by decreased SA- β -Gal activity and lower p16 protein expression [157]. Similarly, compounds such as apigenin, quercetin, kaempferol, and wogonin have been shown to suppress the secretion of SASP markers, including IL-6, IL-8, and IL-1 β [158]. Recent studies by Bientinesi et al. revealed that quercetin can prevent doxorubicin-induced senescence [159,160]. Quercetin not only alleviates the deleterious effects of the SASP in both U2OS and normal cells but also protects fibroblasts from ROS-mediated damage, evidenced by reductions in SAHF, Lamin B1 loss, and NF- κ B nuclear translocation. Moreover, quercetin exhibits senolytic activity, reducing autophagy while increasing endoplasmic reticulum stress, thereby underscoring its multifaceted role in combating cellular aging. Several benefits have also been demonstrated in human in vivo studies. For instance, Maurya et al. showed that in human red blood cells, these flavonoids reduce malondialdehyde (MDA) levels while increasing GSH and membrane sulfhydryl (-SH) group levels [161].

In the context of PD, dietary polyphenols appear to have beneficial effects. Flavonoids, a major subgroup of polyphenols, protect neurons against oxidative stress, suppress neuroinflammation, and modulate key intracellular signaling pathways critical for neuronal survival. These pathways, including protein kinase and lipid kinase signaling cascades, alter the phosphorylation state of target proteins and influence gene expression [162].

Moreover, histochemical evaluations in 6-OHDA-treated mouse models of PD have shown that green tea (a variant of tea obtained with non-treated leaves of *Camellia sinensis*) polyphenols markedly reduce ROS levels, lipid peroxidation, and intracellular nitrite/nitrate concentrations [163,164].

Ginkgo biloba extract has been reported to protect against nigrostriatal dopaminergic neurotoxicity in MPTP-induced PD models, with observed reductions in lipid peroxidation and enhancements in the activities of key antioxidant enzymes such as SOD, GPx, and GSH reductase [165]. Notably, Ginkgo biloba extract inhibited monoamine oxidase B (MAO-B) in vitro, reducing dopaminergic neuron degeneration [165,166].

Resveratrol, a nonflavonoid polyphenol found in grapes and berries, has shown promise in mitigating oxidative stress in PD [167,168] while enhancing the number of dopaminergic neurons at the synapses through MAO suppression as well as the prevention of glutamate release [169–171].

Additionally, oleuropein and its derivatives have been demonstrated to inhibit ROS accumulation and prevent PD pathology. In vitro, oleuropein aglycone stabilizes α -synuclein monomers, thereby preventing pathological aggregation [172], and it also inhibits α -synuclein fibril elongation, reducing the cytotoxic effects of α -synuclein oligomers [173]. Furthermore, oleuropein activates redox-sensitive transcription factors such as Nrf2, which may enhance the intracellular antioxidant capacity and contribute to neuroprotection [174].

Beyond PD, dietary polyphenols have been shown to have several benefits in AD, mitigating pathological manifestations partly due to their ability to cross the blood-brain barrier [175,176]. Oxidative stress plays a pivotal role in the initiation and progression of Alzheimer's, and while the body has evolved defence mechanisms to counteract oxidative damage, aging is associated with increased oxidative stress that disrupts cellular architecture [177]. Polyphenols reinforce endogenous antioxidant defences and attenuate protein oxidation [178]. By sequestering reactive oxygen and nitrogen species, these compounds prevent the formation of toxic A β oligomers and modulate tau-protein hyperphosphorylation, thereby impeding the development of neurofibrillary tangles (NFTs) [179]. Additionally, polyphenols may help preserve neuronal integrity by interacting with transcription factors such as CREB and NF- κ B [180].

Studies on AD transgenic mouse models (APP/PS1 model) and patients' post-mortem brains have revealed a senescent phenotype in oligodendrocyte progenitor cells (OPCs) within the A β plaque environment. Notably, these cells were sensitive to clearance by the senolytic cocktail dasatinib plus quercetin (D+Q). The treatment removed senescent OPCs and ameliorated A β plaque-associated inflammation and cognitive deficits in AD mice. [181]. Meanwhile, in PD, direct evidence of the beneficial effects of D+Q has not been observed, even though some advantages have been shown in the aging killifish [182]. Additionally, fisetin, a natural senolytic, has been shown to improve cognitive function in mouse models of AD and dementia [183]. Among the senolytics tested in multiple preclinical studies and increasing clinical trials, fisetin and D+Q appear to be the most effective [184,185].

Animal studies further substantiate the neuroprotective potential of polyphenols. For instance, mice receiving pomegranate juice exhibited significant improvements in both cued and spatial learning tasks, along with reduced hippocampal plaque loads—including both soluble and fibrillar forms of A β , as well as lower soluble A β ₁₋₄₂ levels [186]. Red wine polyphenols have been shown to interfere with A β oligomerization, thereby attenuating A β neuropathology and cognitive decline in Tg2576 mice [187]. Mori et al. [188] demonstrated that tannic acid shifts amyloid precursor protein metabolism toward a non-amyloidogenic pathway by lowering β -secretase 1 (BACE1) expression and β -secretase activity, decreasing A β peptide levels. Similarly, grape-derived polyphenolics from *Vitis vinifera* grape seeds significantly inhibited A β aggregation in vitro and ameliorated cognitive deterioration in Tg2576 mice when administered orally [189].

Collectively, these findings illustrate the multifaceted neuroprotective potential of dietary polyphenols. By modulating intracellular signaling pathways, gene expression, and enzyme activities, polyphenols offer promising therapeutic avenues for preventing and treating neurodegenerative diseases, highlighting their potential as valuable agents in mitigating age-related cognitive decline and neuronal dysfunction.

4.3. Spices

Over the past decade, numerous studies have underscored various spices' broad spectrum of anti-aging and anti-senescence properties. For instance, the primary bioactive compounds of black pepper, including piperine, chavicine, and sabinene, exhibit significant pharmacological potential. Notably, black pepper oil has reduced the percentage of doxorubicin-induced senescent cells in CHO-K1 and NIH-3T3 cells [190]. Furthermore, curcumin, the primary component of *Curcuma longa*, has

demonstrated a capacity to mitigate age-related deterioration by counteracting oxidative stress [191], modulating inflammatory pathways [192,193], promoting telomere elongation and telomerase activity [194], and influencing key metabolic regulators such as AMPK [195,196] and SIRT6 [197,198]. Similarly, coriander seeds have shown potential in reducing oxidative stress and cellular senescence, as evidenced by decreased expression of senescence markers SA- β -Gal and p21 in cardiac [199] and brain tissues [200] of obese rats.

Beyond their culinary roles, spices have emerged as promising agents for preventing or even counteracting neurodegenerative processes associated with aging. The neuroprotective effects of spices show promising therapeutic potential in PD as well. Curcumin has exhibited multiple protective mechanisms in PD, facilitated by its ability to cross the blood-brain barrier due to its lipophilic nature [201]. Its neuroprotective effects are attributed mainly to its potent antioxidant properties, surpassing conventional antioxidants such as vitamins C and E [202,203]. The ability of curcumin to donate hydrogen ions from its β -diketone moiety is believed to underlie its anti-ROS activity [204]. Notably, pre- or post-treatment with curcumin in 6-OHDA-lesioned rats reduced dopaminergic neuron loss [205], while MES cells treated with curcumin exhibited increased Cu-Zn superoxide dismutase expression and reduced intracellular ROS accumulation [206]. Moreover, curcumin was found to modulate inflammatory processes by decreasing the production of prostaglandins, glutamate, and pro-inflammatory cytokines in the hypothalamus, as well as reducing GFAP levels, a marker of astrocytic proliferation [207].

Similarly, piperine from black pepper has demonstrated neuroprotective effects in PD models. Yang et al. reported that piperine administration ameliorated MPTP-induced motor and cognitive deficits while preventing the loss of tyrosine hydroxylase-positive neurons in the substantia nigra [208]. Additionally, piperine reduced microglial activation, IL-1 β expression, and oxidative stress and exhibited anti-apoptotic properties by modulating the Bcl-2/Bax ratio. Interestingly, piperine has been evaluated in combination with quercetin due to its well-documented ability to enhance the bioavailability of other compounds [209]. Combining quercetin and piperine improved MPTP-induced behavioural and neurochemical deficits while mitigating oxidative stress and inflammation in the striatum [210].

Emerging in vitro evidence further supports the beneficial role of cinnamon and its metabolites in PD. Cinnamaldehyde (10 μ M) was shown to protect BE(2)-M17 human neuroblastoma cells from MPP⁺-induced toxicity by inhibiting autophagy [211]. Cinnamon extract (CEppt) has also shown protective effects against 6-OHDA-induced cytotoxicity by enhancing cell viability, reducing apoptosis, and decreasing ROS levels [212]. Furthermore, CEPpt has been found to interfere with α -synuclein aggregation by stabilizing its soluble oligomeric form and promoting the disassembly of preformed aggregates [213].

In addition to their anti-inflammatory properties, these bioactive compounds exert antioxidative effects and inhibit acetylcholinesterase activity and A β aggregation in AD. Curcumin has demonstrated potent antioxidant activity in both in vitro and in vivo models [214–216]. Epidemiological studies have further revealed an inverse correlation between curcumin intake and AD prevalence, particularly in populations with high dietary consumption of this compound, such as India [217,218]. Mechanistically, curcumin enhances macrophage-mediated clearance of A β plaques [219], suppresses microglial proliferation [220], attenuates neuroinflammation by downregulating pro-inflammatory cytokines [221,222], and inhibits oxidative stress by preventing free radical formation and propagation [223,224]. Remarkably, in vitro studies suggest that curcumin reduces A β levels by modulating APP processing and downregulating BACE1 expression [225]. Additionally, curcumin exhibits a high binding affinity for A β aggregates, thereby preventing their formation both in vitro and in vivo [226].

Beyond curcumin, cinnamon has also demonstrated significant neuroprotective properties. Studies have shown that cinnamon exerts potent antioxidant effects by enhancing the activity of endogenous antioxidant enzymes [227,228] while simultaneously exerting anti-inflammatory effects [229,230]. Notably, a CEPpt effectively inhibits the formation of toxic A β oligomers and protects

neuronal PC12 cells from A β -induced toxicity, eliminating tetrameric A β species in the brain. Moreover, oral administration of this extract in an aggressive AD transgenic mouse model significantly reduced 6 kDa A β oligomers, diminished plaque burden, and improved cognitive performance [231].

Piperine, the principal bioactive component of *Piper nigrum* (black pepper), has been reported to exert neuroprotective effects [232]. In animal models, black pepper administration reduced cholinesterase activity and amyloid plaque formation in the brain [233]. Furthermore, piperine significantly attenuated lipid peroxidation and acetylcholinesterase activity while preserving neuronal density in adult male Wistar rats [232].

Similarly, cardamom oil treatment improved neurobehavioral parameters in male Wistar rats, inhibited acetylcholinesterase activity in the hippocampus and cortex, and enhanced antioxidant enzyme levels while reducing oxidative damage. Additionally, it increased BDNF levels and suppressed A β expression in the hippocampus and cortex [234].

Overall, accumulating evidence suggests that spices such as curcumin, cinnamon, black pepper, and cardamom possess significant neuroprotective properties that may be exploited to prevent and treat neurodegenerative diseases, including AD and PD.

4.4. Dietary Fiber

Recent findings suggest that a high-fiber diet may protect against neurodegenerative disorders by supporting metabolism, modulating neuroinflammation, and regulating epigenetics. Unfortunately, although it displays several effects on key mechanisms of cellular senescence, a direct link to senescence itself remains unclear. Dietary fiber, composed of non-digestible and non-absorbable carbohydrates, influences gut microbiota composition and short-chain fatty acids (SCFAs) production, impacting brain function through the microbiota-gut-brain axis [235,236].

Shi et al. studied dietary fiber deficiency (FD) in mice, revealing alterations in hippocampal synaptic ultrastructure, proteome, and microglial-neuroinflammation pathways, affecting cognition and dopamine cholinergic synapses [235].

Gut microbiome alterations have also been linked to PD, with decreased SCFAs, particularly butyrate, observed in PD patients [237]. Similarly, Matt et al. showed that Butyrate administration and high-fiber diets reduced neuroinflammation in aged mice [238].

For AD, dietary fiber and SCFAs have shown benefits in cholesterol reduction, A β clearance, and neuroinflammation regulation, potentially mitigating A β deposition and brain hypometabolism [239–242].

Furthermore, in vitro studies found valeric, butyric, and propionic acids to interfere with neurotoxic A β aggregation [243], while in vivo, fiber influenced amyloid load in GPCR KO mice, suggesting a role in amyloid metabolism [244].

4.5. Probiotics and Prebiotics

Despite strong evidence supporting the role of probiotics and prebiotics in neuroinflammation and neurodegeneration, their direct impact on cellular senescence remains unclear. However, they have been shown to exert regulatory effects on oxidative stress, inflammation, and metabolism. Notably, they may modulate neuroinflammation, which is at least partially influenced by the presence of senescent cells. Further studies are needed to clarify this relationship and explore their potential in aging and neurodegenerative diseases.

Probiotics and prebiotics influence human health by modulating metabolic regulation, immune response, and neurological function via the gut microbiome [245–249]. Probiotics, particularly *Lactobacilli* species, have demonstrated benefits in aging by enhancing immunity and maintaining gut microbiota balance, potentially extending the healthspan [250–253]. Probiotics can regulate neuroinflammation and oxidative stress in neurodegenerative diseases, reducing the risk of disorders like PD and AD [254–257].

In PD, probiotics improve gut health, mitigate permeability, and reduce neuroinflammation [258]. Cellular studies show that probiotic treatment can shift cytokine production towards an anti-inflammatory profile [259], while in vivo studies suggest protection against dopaminergic neuron loss and neurotrophic factor depletion [260–262]. Similarly, specific probiotic strains can restore gut microbiota balance in AD, improve cognitive function, and mitigate pathological features such as A β deposition and oxidative stress [263,264]. However, the precise mechanisms remain unclear [265,266], and probiotics' role as modulators of cellular senescence per se is only beginning to be understood.

Conversely, prebiotics, including fructo- and galacto-oligosaccharides, promote SCFA production and support cognitive function [267]. They modulate oxidative damage, enhance GLP-1 (glucagon-like peptide 1) secretion, and potentially regulate brain glucose metabolism and CNS inflammation via GLP-1 receptors [268,269]. Prebiotics alter gut microbiota composition in PD, reducing pro-inflammatory bacteria and increasing SCFA-producing taxa, with promising neuroprotective effects [270,271]. Intriguingly, their combination with probiotics appears particularly beneficial [272,273].

On the other hand, prebiotic supplementation in AD models has shown improvements in neurotransmitter levels, cognitive function, and A β pathology, with chitosan oligosaccharides demonstrating neuroprotective properties in several studies [274].

4.6. Polyunsaturated Fatty Acids (PUFAs)

PUFAs are crucial in neuroprotection, presenting potential therapeutic implications for neurodegenerative diseases. Evidence supports their involvement in modulating inflammation, oxidative stress, and neurotoxicity. However, further research is required to investigate their direct action as senolytic or senostatic agents and their influence on the broader aging process [275]. PUFAs play a fundamental role in neurodevelopment, neurotransmission, and neuromodulation, with potential neuroprotective effects that include reducing neuroinflammation, mitigating neurotoxicity, promoting neural recovery, and preserving blood-brain barrier integrity [276].

Among PUFAs, omega-3 (n-3) and omega-6 (n-6) long-chain polyunsaturated fatty acids (LCPUFAs) are essential for brain function, constituting 30–35% of total brain fatty acids. Docosahexaenoic acid (DHA) and AA are the predominant LCPUFAs in phospholipids, playing key roles in synaptic integrity, plasticity, and cognitive function [277,278]. Neuroinflammation is a major contributor to age-related neurodegeneration, and n-3 LCPUFAs, particularly eicosapentaenoic acid (EPA) and DHA, exhibit anti-inflammatory properties by downregulating IL-6 and TNF- α while enhancing cognitive function [279]. Interestingly, higher brain DHA concentrations correlate with improved cognitive performance, likely due to its effects on membrane fluidity, neurotransmitter release, gene expression, neuroinflammation, and neuronal growth [280,281]. These fatty acids also possess antioxidant and anti-apoptotic effects, mitigating neurotoxicity in preclinical models [282,283].

Research on dietary fats is still emerging in PD, but observational studies suggest that LCPUFA intake may offer neuroprotection [284,285]. For example, a meta-analysis reported that higher LCPUFA consumption is associated with a reduced PD risk, while specific plasma fatty acid levels correlate with motor and non-motor symptoms [286]. Additionally, n-3 PUFAs have demonstrated neuroprotective effects in MPTP-induced PD mice models, preventing neuronal loss and preserving striatal dopamine levels [283,287–290].

In AD, epidemiological studies and randomized controlled trials (RCTs) indicate that higher n-3 LCPUFA intake correlates with a lower incidence of cognitive impairment and dementia [281,291]. Other RCTs in individuals with mild to moderate AD have reported cognitive improvements following supplementation [292,293]. Animal studies suggest DHA reduces amyloid accumulation, tau pathology, and synaptic dysfunction, with several independent reports confirming reduced A β levels in APP transgenic models following DHA-enriched diets [294–298].

5. Conclusions

The review highlights the important role of nutraceuticals and functional foods in reducing aging and neurodegenerative diseases by modulating cellular senescence. It discusses how these natural bioactive compounds possess potent antioxidant, anti-inflammatory, and epigenetic properties that can impact essential cellular pathways associated with aging and the onset of neurodegenerative diseases. We specifically emphasize the importance of polyphenols, vitamins, and spices as nutritional senotherapeutic agents in scavenging ROS, reducing the secretion of inflammatory SASP factors and modulating gene expression alongside other characteristics related to cell senescence (Figure 3).

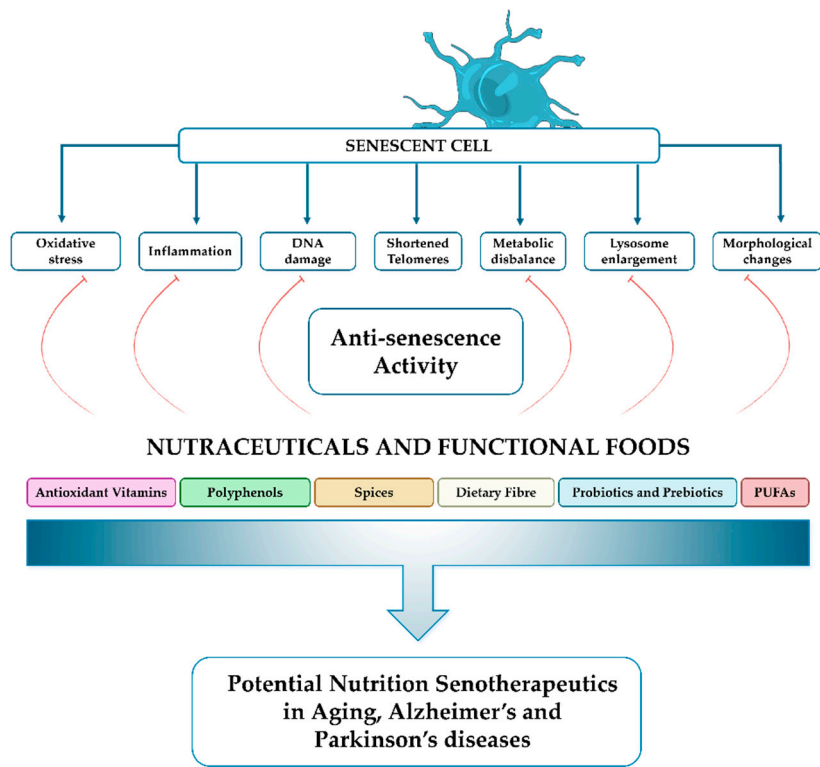


Figure 3. The Benefits of Nutraceuticals and Functional Foods in Aging and Neurodegenerative Diseases. Nutraceuticals and functional foods are crucial in combatting aging, providing a natural and accessible approach to promoting longevity and healthspan. Among the most researched bioactive compounds are antioxidant vitamins, polyphenols, spices, dietary fiber, probiotics, prebiotics, and PUFAs. These substances offer protective and rejuvenating effects at the cellular level, helping to alleviate the hallmarks of aging and the harmful traits of senescent cells. Nutraceuticals can support cellular homeostasis and slow down age-related functional decline by reducing oxidative stress, moderating chronic inflammation, preserving DNA integrity, preventing telomere shortening, and restoring metabolic balance. Additionally, they aid in maintaining lysosomal function and guarding against the structural changes associated with senescence, including morphological alterations and cellular enlargement. Through their diverse mechanisms of action, these bioactive compounds assist in delaying aging and reducing the risk of ARDs, such as neurodegeneration.

Collectively, these actions contribute to alleviating cellular damage that is involved in both aging and the onset of neurodegenerative disorders such as AD and PD diseases.

Furthermore, the review highlights that substantial evidence supports the beneficial effects of these nutraceuticals on cellular processes, such as improving mitochondrial function, reducing oxidative stress, and modulating inflammatory responses, direct evidence demonstrating a senolytic effect is still limited.

Most existing studies have primarily focused on elucidating the mechanisms through which these compounds influence senescence-associated characteristics rather than proving a direct reduction of the number of senescent cells. This emerging and relatively new field requires further

research to explore these correlations in more detail and to understand the potential benefits of introducing nutraceuticals into preventive strategies. Such interventions may offer a promising approach to extending healthspan by targeting the underlying mechanisms of cellular senescence, although current research is still in its infancy. Ultimately, the review suggests that including nutraceuticals in comprehensive dietary interventions may help lower the risk of neurodegenerative diseases. However, the scarcity of clinical data raises questions about their effectiveness, especially considering the emerging hormetic properties of certain nutraceuticals.

Numerous questions remain unresolved regarding the application of nutraceuticals as senotherapeutics, but there exists a pressing necessity to identify anti-aging strategies that promote active longevity while minimizing disability and functional dependence.

Author Contributions: Conceptualization, S.R., G.B., E.B. and D.M.; writing—original draft preparation, S.R., G.B.; writing—review and editing, E.B. and D.M, supervision and funding acquisition: D.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by co-funding from the European Union – Next Generation EU, in the context of The National Recovery and Resilience Plan, Investment Partenariato Esteso PE8 “Conseguenze e sfide dell’invecchiamento”, Project Age-IT, CUP: B83C22004800006, to D.M.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: We acknowledge co-funding from Next Generation EU, in the context of the National Recovery and Resilience Plan, Investment PE8 – Project Age-It: “Ageing Well in an Ageing Society”. This resource was co-financed by the Next Generation EU [DM 1557 11.10.2022]. The views and opinions expressed are only those of the authors and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

αT	α-tocopherol
αTP	α-tocopheryl phosphate
Aβ	Amyloid-β peptide
AA	Arachidonic acid
AAC	Ascorbic acid
AD	Alzheimer’s Disease
ARDs	Age-related diseases
BACE1	β-secretase 1
CEppt	Cinnamon extract
CNS	Central Nervous System
CR	Caloric Restriction
D+Q	Dasatinib plus Quercetin
DHA	Docosahexaenoic Acid
DOPA	Dihydroxyphenylalanine
EPA	Eicosapentaenoic Acid
FD	Fiber deficiency
GLP-1	Glucagon-like peptide 1
GSH	Glutathione
GSs	Geriatric Syndromes
IL	Interleukin
LCPUFAs	Long-chain polyunsaturated fatty acids
MAO-B	Monoamine Oxidase B
MDA	Malondialdehyde
MedDiet	Mediterranean Diet

MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NFTs	Neurofibrillary tangles
PD	Parkinson's Disease
PUFAs	Polyunsaturated Fatty Acids
ROS	Reactive Oxygen Species
SASP	Senescence-Associated Secretory Phenotype
SA- β -gal	Senescence-Associated β -Galactosidase
SAHFs	Senescence-associated heterochromatic foci
SCFAs	Short-Chain Fatty Acids
SIRT	Sirtuin

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