nutrients

MDPI

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

Sara Ristori †, Gianmarco Bertoni †, Elisa Bientinesi and Daniela Monti *

Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, 50134 Florence, Italy; sara.ristori@unifi.it (S.R.); gianmarco.bertoni@unifi.it (G.B.); elisa.bientinesi@unifi.it (E.B.)

* Correspondence: daniela.monti@unifi.it; Tel.: +39-0552751301

† These authors contributed equally to this work.

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 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 bioactive compounds 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

Academic Editor: Dominik Szwajgier

Received: 7 April 2025
Revised: 13 May 2025
Accepted: 22 May 2025
Published: 28 May 2025

Citation: Ristori, S.; Bertoni, G.; Bientinesi, E.; Monti, D. 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. *Nutrients* **2025**, *17*, 1837. https://doi.org/10.3390/nu17111837

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

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.

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 [13]. Which determinants make aging trajectories more or less steep? Environmental conditions, such as the intensity and types of stressors, as well as 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. Hormesis refers to the beneficial effects of cellular responses to mild, repeated stress [15,16]. This theory suggests that regular exposure to mild stressors can positively impact various organs and systems, including adipose tissue, the liver, the brain, and the immune system [15], ultimately leading to enhanced overall

health. 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 [17].

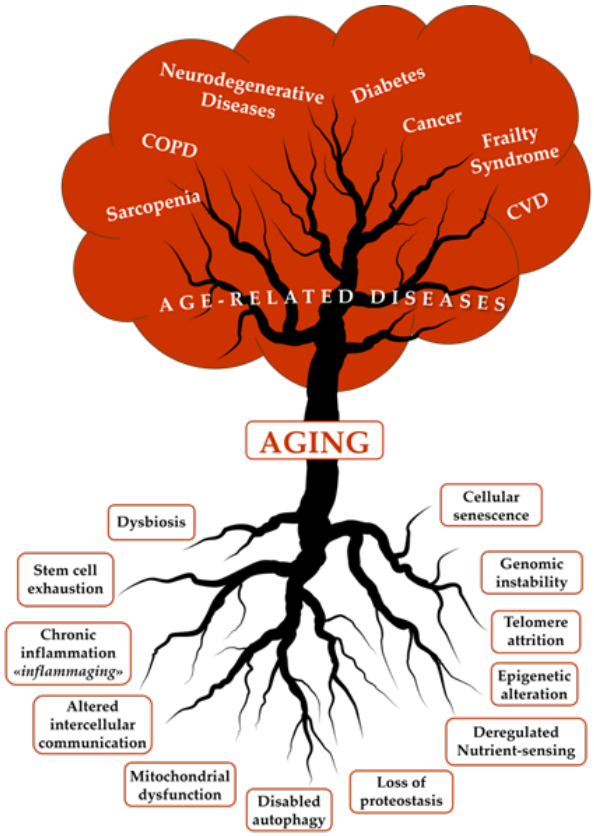

Figure 1. The hallmarks of aging. Aging is a multifactorial process at various levels, from molecules to cells, organs to systems, ultimately affecting the entire organism. In 2023, López-Otín and colleagues refined the framework of aging hallmarks, identifying 12 key features: dysbiosis, stem cell exhaustion, 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 [12].

A recent multi-omics data study has shown that different organs and tissues can age at distinct rates within the same individual [18]. Brain pathologies and changes in brain structure are commonly seen in aging [19], with significant modifications in the brain's intricate microstructure resulting in cognitive decline [20]. Brain morphology evolves with age and most commonly undergoes significant atrophy [21]. These changes are associated with, if not directly the cause of, cognitive deficits such as memory loss [22,23], reduced motor performance [24], and alterations in behavior [25].

Among neurodegenerative diseases, Parkinson's disease (PD) and Alzheimer's disease (AD) are the most common. Usually, they have a late debut of 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 in 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 increased cognitive decline and the risk of AD and PD [26].

This article comprehensively reviews recent advancements concerning the impact of various nutraceuticals and foods on cellular senescence and its interconnected aspects. 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.

A narrative search was conducted across multiple databases, including PubMed, Scopus, Web of Science, and Google Scholar, to gather the relevant literature for this review. The search utilized the following keyword combinations: "Antioxidant vitamins OR Polyphenols OR Spices OR Dietary Fibers OR Probiotics OR Prebiotics OR PUFAS OR Diets OR Mediterranean Diet OR Caloric Restriction AND Aging AND Cellular Senescence OR Neurodegeneration OR Alzheimer's disease OR Parkinson's disease". The search included only articles published in English and those available via open access to ensure the inclusion of the most recent advancements. Studies included in the review were required to focus on preclinical (in vitro and in vivo experiments) and clinical studies, specifically addressing how nutraceuticals influence the mechanisms of cellular senescence in aging and neurodegenerative diseases. Additionally, the review cites papers considered pioneering in the field.

2. The Role of Senescence in Aging and Neurodegenerative Diseases

Senescence is considered a highly dynamic, multistep process over which the properties of senescent cells continuously evolve and diversify context-dependently [27]. 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 [28]. Subsequent studies have proven that a variety of stressors, including oxidative stress, DNA damage, oncogene activation, mitochondria deterioration, chemotherapy, and exposure to ionizing radiation (IR), can trigger "stress-induced premature senescence" in vitro [29,30].

Senescence activation leads to several molecular changes and distinct phenotypic alterations, including chromatin remodeling, shortened telomeres, the accumulation of DNA damage and reactive oxygen species (ROS), the activation of cell-cycle inhibitory pathways, lysosome enlargement, macromolecular disruption, metabolic disbalance, apoptosis resistance, and the SASP [31]. The SASP is characterized by the synthesis of 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 [30] (Figure 2).

As the number of senescent cells increases with age, there is increasing evidence suggesting their involvement in the pathogenesis of ARDs [32–34], including neurodegenerative diseases such as AD and PD [35].

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 [36]. It has been reported that the final dysfunction and neuronal loss observed in neurodegenerative diseases are often accompanied 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 neuropathogenesis [37–39].

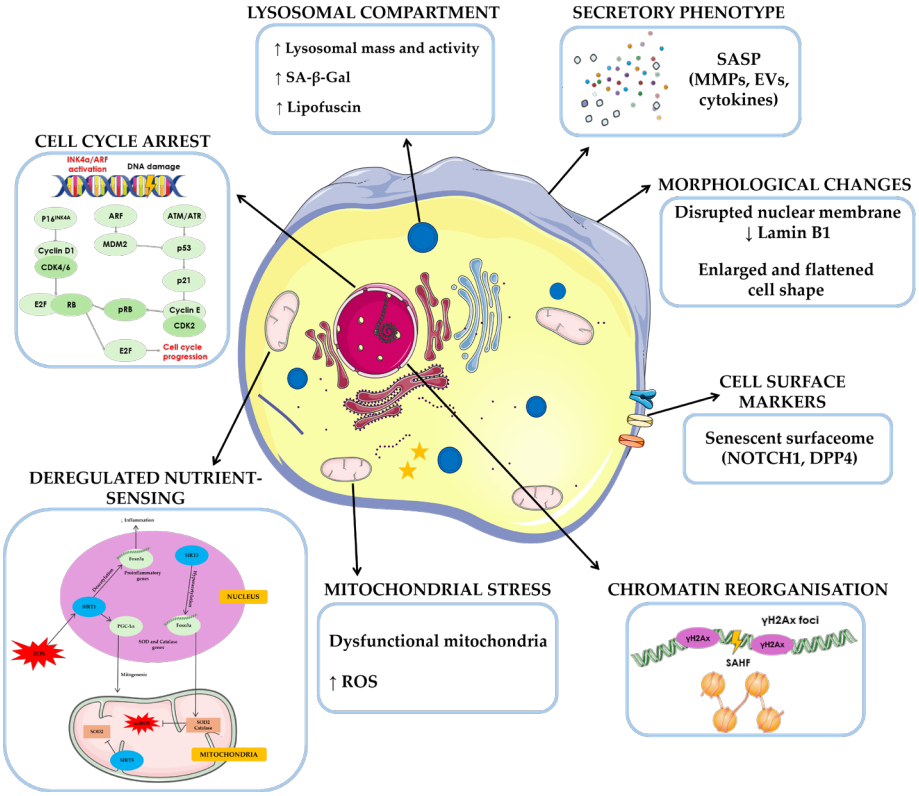

Figure 2. The hallmarks of cellular senescence. Senescent cells undergo distinct morphological and molecular alterations defining cellular senescence's hallmarks. At the genomic level, senescence is characterized by stable cell-cycle arrest, primarily driven by the $p16^{INK4a}$/Rb and $p21^{CIP1}$/p53 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-1α 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-1β, IL-6, TNF-α, etc.) and matrix metalloproteinases (MMPs), often encapsulated in extracellular vesicles (EVs). ↑ increase; ↓ decrease.

Evidence shows that senescent astrocytes accumulate in AD and PD patients, promoting inflammation through the SASP factors [40–42]. Indeed, several SASP factors, including MMP-3, IL-1α, IL-6, and IL-8, are increased in PD and AD brains, indicating that cellular

senescence could contribute to neurodegeneration [35,43,44]. 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 [44]. Conversely, the attenuation or elimination of cellular senescence has been shown to alleviate neuroinflammation in AD and PD models [43,45]. Moreover, a recent study revealed that senescent neurons with tau neuropathology are prevalent in patients with AD [46], while the removal of accumulated senescent glial cells attenuated cognitive decline and age-related neurogenerative disorders [47].

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 [39].

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 [48]. 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 the accumulation of senescent cells or enhance the ability of cells, tissues, or the organism to repair or adapt to this damage [49]. 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" [50]. As discussed in the following 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 [51].

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. Recent findings show that several natural compounds may act in a hormetic-like manner. These hormetic compounds may mediate health-promoting actions by triggering one or more adaptive stress response pathways [52]. This phenomenon is particularly evident among polyphenols, such as curcumin and resveratrol [53,54]. Interestingly, combining different nutraceuticals, such as probiotics and polyphenols, a hormetic nutritional approach, exerts potent neuroprotective and therapeutic effects by activating antioxidant Nrf2 signaling pathways. Consequently, these hormetic nutrients may prevent and treat inflammation-driven pathophysiological changes in gut microbiota diversity that contribute to nervous system disorders via the gut-brain axis [54]. Reading the following reviews can comprehensively understand the topic [55–57].

Recent studies have focused on discovering nutraceuticals that mimic the effects of metformin and rapamycin, inhibiting mTOR, without their side effects. Researchers have individuated withaferin A, allantoin, ginsenoside, and epigallocatechin gallate as promising candidates for experimental validation [58,59]. These substances induced strong activation

of the cAMP pathway, which was recently found to induce anti-aging effects similar to caloric restriction (CR) via the up-regulation of sirtuins (SIRTs) [60]. SIRTs, 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 [61–63].

CR consists of a 25–50% calorie reduction compared to a standard diet, with preservation of vitamin and mineral supply [64]. In addition to SIRTs, 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 [65]. Experimental studies have reported that CR reduces molecular features of cellular senescence in different human and mouse models [33,66,67]. 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 [68]. Moreover, dietary restriction and plant-based dietary patterns have been linked to improved key clinical outcomes related to aging, particularly body composition changes, lipid profile, blood pressure, lipid peroxidation, inflammation, and cardiometabolic risk [66,69–75]. 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 [76]. Conversely, in older adults, CR may exacerbate sarcopenia and osteopenia, contributing to muscle and bone loss [77].

In addition to CR, other dietary patterns have been proposed to promote healthy aging with hormetic behavior [78,79]. Among these, the Mediterranean diet (MedDiet) is the most studied. The 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 [80–84] and reducing cognitive impairment [85]. Intriguingly, emerging proofs suggest that adherence to the MedDiet may contribute to delaying cellular senescence [86]. In older adults, adherence to the MedDiet has been associated with a lower proportion of endothelial cells with shorter telomeres, an effect likely mediated by decreased ROS production and apoptosis [87]. Similarly, Mantilla-Escalante suggests that long-term adherence (1 year) to the Med-Diet, particularly when enriched with nuts, can modulate the expression of several mi-croRNAs (miRNAs) involved in cellular senescence, including cell-cycle regulators and pro-inflammatory markers. The MedDiet, through miRNA-mediated gene modulation, may influence fundamental mechanisms of aging and cellular homeostasis [88].

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 [89,90].

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 [91].

Additionally, an intriguing hypothesis suggests that bioactive compounds in food may extend healthspan by modulating the SASP, indicating new strategies to slow the onset and progression of ARDs [92]. 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 [93–95].

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 [96]. This category includes conventional foods enriched with bioactive compounds such as vitamins, minerals, and phytochemicals [91,92], directly impacting nutritional health by enhancing overall well-being or reducing disease risk [97]. 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 [98]. Martucci et al. studied, through an interventional trial with 48 elderly volunteers, the impact of fortified milk on inflammaging parameters. 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 ratios [99]. Yoghurt, rich in anti-inflammatory and B-vitamin content, may help protect against cognitive decline. Tillisch et al. showed in a randomized trial on healthy women that a four-week intake of fermented milk affected brain function changes [100].

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 [101].

Due to modulating many biological mechanisms in mammalian bodies and cells, the following anti-aging mechanisms of functional foods could be proposed: (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 [102–105].

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 [106].

Therefore, countering and removing senescent cells in the brain, or at least postponing their senescence and alleviating the adverse effects of a spreading SASP, could be a strategy for helping to slow the progression of AD and PD or delaying their onset.

This section 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 compounds that demonstrate 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 origin. The results from studies on their effects as senotherapeutic substances in aging and neurodegenerative diseases are presented below and summarized in Table 1.

Table 1. Overview of nutraceutical compounds studied in the context of aging and neurodegenerative diseases. Experimental models, effects (mechanisms of action), observations, and corresponding references are reported for each compound. Abbreviations: dUCH: ubiquitin C-terminal hydrolase; LTP: Long-Term Potentiation; LTD: Long-Term Depression; PINK1: PTEN-induced kinase 1; MMP+: 1-Methyl-4-phenylpyridinium; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; RBC: red blood cells; t-BHP: tert-Butyl hydroperoxide; MDA: malondialdehyde; OPC: Oligodendrocyte Precursor Cells; GPx: Glutathione Peroxidase; 6-OHDA: 6-Hydroxydopamine; TBARS: Thiobarbituric Acid Reactive Substances; DA-D2: Dopamine D2 receptor; SAMP8: senescence-accelerated prone 8; hTERT: human Telomerase Reverse Transcriptase; TH: Tyrosine Hydroxylase; ΔΨm: Mitochondrial membrane potential; PBMC: Peripheral Blood Mononuclear Cells; swAPP: Swedish Amyloid Precursor Protein; AChE: Acetylcholinesterase; SCFA: Short-Chain Fatty Acids; MAO B: Monoamine Oxidase B; TTR: Transthyretin; DHA: Docosahexaenoic Acid; AA: arachidonic acid; hNT: human Neural Tissue; HO-1: Heme Oxygenase-1; DI TNC1: Rat type 1 astrocytes; H 19–7: rat hippocampal neurons; QR: Quinone reductase; GSTs: Glutathione S-transferase; N2a: Mouse neuroblastoma-derived cells; ADAM(10): metalloproteinase; ALDH1A1: Aldehyde dehydrogenase 1A1; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine; MMSE: Mini–Mental State Examination; Ceppt: cinnamon extract; AS-IV: Astragaloside IV.

Nutraceuticals	Study Models	Effects	Observations	References
Antioxidant vitamins				
Vitamin C	Albino mice	Improves memory	↓ Acetylcholinesterase activity	[107]
	Drosophila dUCH Drosophila DJ-1β mutant (PD models)	Neuroprotective	↓ Dopaminergic neuron loss	[108] [109]
	SH-SY5Y cells ($A\beta_{25-35}$ -treated)	Protects cells from $A\beta_{25-35}$-mediated apoptosis	↓ Basal Aβ secretion	[110]

Table 1. *Cont.*

Nutraceuticals	Study Models	Effects	Observations	References
	Wistar rats Aβ- or artificial cerebrospinal fluid-injected (AD models)	↓ Oxidative stress ↓ Neuroinflammation	↓ Lipid peroxidation products ↓ IL-1β, IL-6, and TNFα	[111]
	Hs68 human dermal fibroblasts, H_2O_2-treated Middle-aged hairless mice, LPS-treated hAPCs	Prevents cellular senescence	↓ Hyperactivation of PI3K/AKT ↓ p53/p21 ↓pRB/p16 ↑ E2F1/E2F2 ↓ mTOR ↑ FoxO3a ↑ SIRT1	[112] [113]
Vitamin E	Questionnaire-based case–control study (healthy and PD patients) Brain slice of PINK1$^{-}/^{-}$ mice	Reduces PD occurrence Reverses impaired synaptic plasticity	Restored LTD and LTP	[114]
	Drosophila DJ-1β mutant (PD model)	↓ Oxidative stress ↑ Lifespan	↑ Catalase activity ↓ SOD	[109]
	SH-SY5Y cells treated with MPP+, MG132, and thapsigargin (PD model) Mice, MPTP-treated (PD model)	Neuroprotective against PD-related toxicities Antioxidant effects ↑ Motor function	Activation of ERβ/PI3K/Akt pathway	[115] [116]
	C57 black mice, MPTP-treated (PD model)	Prevent neuronal loss in substantia nigra	↓ Striatal dopamine loss	[117]
	Cross-sectional study (>40 years old)	Reduced risk of PD	-	[118]
	Primary rat embryonic hippocampal neurons, $A\beta_{1-42}$-treated (AD model)	↓ Oxidative stress	Prevents $A\beta_{1-42}$-induced neuronal protein oxidation Free-radical scavenger	[119]
	IL-1β-stimulated A549 cells LPS-stimulated RAW264.7 macrophages (inflammatory diseases model)	↓ Inflammation	↓ PGE_2 COX_2 inhibition	[120] [121]
	HUVECs Human primary dermal fibroblasts (replicative senescence) Human primary skin fibroblasts from young and aged subjects	Delays senescence	↓ Number of senescent cells ↓ p21	[122] [123]
Vitamin A	HEK293 cells	Cytoprotection	Inhibits Aβ oligomer formation	[124]
	Cortical neurons from embryonic mice, $A\beta_{1-40}$- and $A\beta_{1-42}$-treated 129S2/SvHsd and Tg2576 mice (AD models)	Neuroprotective	Inhibits Aβ oligomer formation ↑ Disintegrin ↑ADAM (10) ↑ TH	[125]
	SH-SY5Y cells	Hormetic effect ↓ Oxidative stress	↑ Akt and ERK1/2 phosphorylation	[126]
	Postnatal and adult Aldh1a1 knockout mice	↓ Dyskinesia	↑ MOR1	[127]

Table 1. *Cont.*

Nutraceuticals	Study Models	Effects	Observations	References
Vitamin B	AD patients	Cognitive improvement ↓ Neuroinflammation	↑ MMSE ↑ SAM/SAH ↓ $A\beta_{1-40}$, PS1, and TNFα ↓ Blood homocysteine	[128] [129]
	SAMP8 mice Astrocytes from mice (Aging models)	↓ Neurodegeneration	↑ Telomerase activity ↓ Astrocitosis ↓ Apoptosis	[130]
	Gibco Human Astrocytes Vitamin-B12-deficient	↓ Senescence	↓ SA-β-Gal, p16, p21	[131]
Polyphenols, Terpenes, and Terpenoids				
Quercetin	WI-38 fibroblasts (Doxo-treated)	Prevents cellular senescence ↓ Senescent fibroblast pro-tumor effects	↑ SOD1 and SOD2	[132]
	WI-38 fibroblasts	Senolytic effect	↓ Autophagy ↑ ER stress	[133]
	Human RBC cells, *t*-BHP-treated (oxidative stress model)	↓ Deleterious effects of oxidative stress in erythrocytes	↓ MDA ↑ GSH ↑ Membrane-SH Group	[134]
Quercetin + Dasatinib	$A\beta_{1-42}$-induced senescent OPC cells APP/PS1 transgenic mice (AD model)	Senolysis of senescent OPCs ↓ Neuroinflammation ↑ Cognitive function	Inflammation, senescence, Aβ pathology	[135]
Ginkgolides and bilobalide	C57BL/6J mice, MPTP-treated (PD model)	Protect against nigrostriatal dopaminergic neurotoxicity ↑ Locomotion activity ↓ Oxidative stress	↓ Lipid peroxidation ↓ Mn-SOD ↑ GPx activity ↑ Glutathione reductase Inhibitory effect of brain	[136] [137]
Resveratrol	Wistar rats, 6-OHDA-treated (PD model)	↑ Antioxidant status ↓ Dopamine loss	↓ TBARS ↑ GSH, TH, Na^+/K^+-ATPase activity ↓ DA-D2 receptor binding ↓ PLA2 and COX-2	[138]
	SK-N-BE cells, 6-OHDA-, $A\beta_{1-42}$-, and α-sin-treated (oxidative stress, PD, and AD models)	Neuroprotection ↓ Oxidative stress	Activates SIRT1 ↑ Autophagy	[139]
Oleuropein	SH-SY5Y and OLN-93 cells, α-synuclein-treated (PD models)	Stabilizes α-synuclein monomers Prevents pathological aggregation ↓ Cytotoxicity ↓ Oxidative stress	↑ α-Synuclein proteolysis ↓ α-Synuclein interaction with cell membrane ↓ LDH release	[140] [141]

Table 1. *Cont.*

Nutraceuticals	Study Models	Effects	Observations	References
Fisetin	Aged SAMP8 mice (AD model)	Prevents cognitive and locomotor deficits with age ↓ Neuroinflammation	↓ SAPK/JNK Metabolic alteration	[142]
Limonene	Adult Mediterranean fruit flies (aging model)	↑ Lifespan	Hormetic effect	[143]
Ginsenoside F1	Human astroglioma CRT and U373-MG cells (20 g/L D-galactose-induced senescence)	Suppresses the SASP ↓ Astrocyte-derived neuroinflammation	↓ p38MAPK-dependent Nf-κB	[144]
	Mouse sw APP N2a cells (AD model)	Reduces $A\beta_{1-40}$ and $A\beta_{1-42}$ formation	↑ PPARγ ↓ BACE1	[145]
Artemisin	LPS-activated RAW 264.7 macrophages	↓ Inflammation	↓ AChE	[146]
AS-IV	Replicative-induced and LPS/MPP^+-induced senescent mouse astrocytes Mice, MPTP-treated (PD models)	↓ Inflammation Neuroprotection ↑ Longevity ↓ Dopaminergic neuron loss	Attenuates senescence and SASP ↑ TH ↑ Autophagy	[147]
Spices *Curcumin*	Astrocytes DI TNC1 and neurons H 19–7 from rats	Cytoprotection against oxidative stress	↑ HO-1 and Nrf2 ↑ QR and GSTs	[148]
	Human AD and Tg2576 mouse brain sections swAPP Tg2576 transgenic mice (AD model) Differentiated SH-SY5Y cells, Aβ-treated (AD model)	Blocks Aβ aggregation Prevents Aβ cytotoxicity	Labels amyloid plaques in the brain Induces disaggregation of pre-aggregated Aβ	[149]
	HEK293T (hTERT-transfected)	↑ Telomere elongation	↑ Telomerase activity	[150]
	Sprague Dawley rats, 6-OHDA-treated (PD model)	Neuroprotective	↓ Loss of TH-positive cells and DA content	[151]
	MES23.5 cells, 6-OHDA-treated (PD model)	Protects from neurotoxicity	Restores ΔΨm ↑ Cu-Zn SOD ↓ ROS ↓ NF-κB activation	[152]
	PBMC from healthy and AD patients	↑ Aβ clearance	↑ AD macrophage-mediated Aβ phagocytosis	[153]
	PC12 rat cells and HUVECs, Aβ-treated (AD model)	Protects from $A\beta_{1-42}$ insult	↑ Antioxidant pathway	[154]
	swAPP HEK293 cells (AD model)	↓ $A\beta_{1-42}$ production	↓ APP protein expression	[155]
	In vitro *(cell-free)*	Inhibits aggregation	Inhibits $A\beta_{1-40}$ and $A\beta_{1-42}$ fibril formation and extension	[156]

Table 1. *Cont.*

Nutraceuticals	Study Models	Effects	Observations	References
Piperine	C57BL/6 mice, MPTP-treated (PD model)	↓ MPTP-induced deficits in motor coordination and cognitive functioning Prevents decrease in TH-positive cells	↑ Bcl2/Bax ratio ↓ Oxidative stress ↓ Microglia activation ↓ IL-1β	[157]
	Wistar rats, AF64A-injected (AD model)	Improves memory impairment and neurodegeneration in hippocampus	↓ Lipid peroxidation ↓ AChE activity	[158]
	Albino rats, aluminum-chloride-injected (AD model)	Prevents neurodegeneration ↑ Memory	↓ AChE activity	[159]
Cinnamaldehyde and CEppt	BE(2)-M17 cells	Prevents neuronal death in the substantia nigra	Autophagy	[160]
	PC12 cells (6-OHDA-treated)	Protective against 6-OHDA-induced cytotoxicity	↑ Survivin ↓ Cyt-c Oxidative stress, apoptosis	[161]
	Drosophila mutated for A53T α-synuclein in the brain (model of PD)	Neuroprotective	Interferes with α-synuclein aggregation Promotes disassembly of performed aggregates	[162]
	THP-1 monocytes, LPS-treated (inflammatory model)	↓ Inflammation	↓ Akt and IκBα phosphorylation	[163]
	PC12 cells, Aβ-treated Drosophila, $A\beta_{42}$-transfected 5XFAD mice (AD models)	Inhibits formation of toxic Aβ oligomers Improves cognitive behavior Ameliorates locomotion defects	Prevents Aβ cytotoxicity Aβ aggregation ↓ Aβ plaques	[164]
Cardamom oil	Wistar rats, aluminum-chloride-injected (AD model)	Improves behavioral parameters ↓ Oxidative stress ↓Neuronal damage ↓ Aβ plaques	↓ AChE activity	[165]
Dietary Fiber				
	Adult and aged Balb/c mice	↓ Inflammatory infiltrate	↑ Butyrate gut microbiota ↑ SCFA production	[166]
	In vitro *(cell-free)*	Inhibits $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ aggregation	Protein interaction	[167]
	5xFAD mice (AD model)	Delays cognitive decline ↑ Cognitive function ↑ Memory	Alters microglial transcriptome Alters T-cell profile in the brain	[168]

Table 1. *Cont.*

Nutraceuticals	Study Models	Effects	Observations	References
Probiotics				
	Accelerated-aging C57BL/6 mice	↓ Inflammation ↑ Neurotrophic factor ↑ Memory	↓ p16, NF-κB, iNOS, and COX-[2]	[169]
	C. elegans, H_2O_2-treated HT-29 cells stimulated with proinflammatory cytokines	↑ Lifespan Anti-inflammatory ↓ Oxidative stress	Modulation of DAF[2]/DAF-[16] pathway	[170]
	D-galactose-induced oxidative stress, ICR mice	↑ Antioxidant status ↓ Liver damage ↓ Lipid peroxidation	↑ Nrf[2]/Keap[1] ↑ SOD ↑ GPx	[171]
	PBMCs from healthy and PD patients	↓ Inflammation ↓ Oxidative stress ↑ Anti-inflammation	Restore membrane integrity ↓ Pathogenic bacteria	[172]
	SH-SY5Y cells (dopaminergic phenotype) C57BL/6 mice, 6-OHDA-treated (PD models)	↑ Synaptic plasticity ↑ Neuroprotection ↓ Neuroinflammation	↑ PI[3]K/Akt, NF-κB, and PPARγ ↓ JNK/ERK	[173]
	C57BL/6 mice, MPTP- and rotenone-treated (PD models)	↓ Motor deficits ↓ Neuroinflammation ↓ Oxidative stress Neuroprotective	↑ Neurotrophic factors and butyrate level ↓ Glial reactivity Antioxidant enzymes Gut microbiota ↓ Dopaminergic neuronal death ↓ MAO B	[174] [175]
	Aged Fischer 344 rats	↓ Inflammation Ameliorate age-dependent memory impairment	↓ NF-κB ↓ p[16], COX-[2], and iNOS in the hippocampus	[176]
	ddY-mice, $A\beta_{1\text{-}42}$-injected (AD model)	↓ Inflammation Prevent cognitive dysfunction	↓ Immune-reactive-related genes	[177]
Prebiotics				
	Healthy and PD patients	↓ Inflammation ↓ Neurodegeneration ↓ Non-motor symptoms	↑ Beneficial metabolites Change microbiota	[178] [179]
	D-galactose- and $A\beta_{1\text{-}42}$-induced deficient Sprague Dawley rats (AD model)	↓ Oxidative stress ↓ Inflammation ↑ Learning and memory abilities	↓ Tau and $A\beta_{1\text{-}42}$ expression Modulate microbiota–gut–brain axis	[180]

Table 1. *Cont.*

Nutraceuticals	Study Models	Effects	Observations	References
PUFAs				
	C57BL/6 mice, MPTP-treated (PD model)	Neuroprotective	Prevent decrease in TH-labeled nigral cells Protect from dopamine decrease	[181]
	Human subjects (>55 years old) PD patients	Lower the risk of PD	Modify the association of PD with paraquat and rotenone	[182] [183]
	C57BL/6 mice, MPTP-treated (PD model)	Neuroprotective	↑ BDNF	[184]
	Wistar rats, Aβ-treated (AD model)	Neuroprotective	↓ ROS, NOX1, MAO ↑ NOX2, DOS1, serotonine Prevent the ↓ of IL-10	[185]
	AD patients	Reduce Aβ in the brain	↑ TTR that binds and reduces Aβ	[186]
	Aged transgenic Tg2576 mice (AD model)	Neuroprotective	↑ PI3K/Akt ↓ BAD	[187]
	Old 3xTg AD mice	Ameliorate cognitive performance	Ameliorate DHA/AA balance	[188]
	5XFAD mice (AD model) Mouse astrocytes and microglia, LPS-stimulated	↓ Inflammation Ameliorate cognitive deficits	↓ Soluble form of Aβ ↑ Abca1 and ApoE gene expression	[189]
	swAPP/PS1ΔE9 tg mice hNT neuronal cultures (AD models)	Prevent amyloid toxicity	↓ Plaque ↑ Drebrin in hippocampus	[190]

4.1. Antioxidant Vitamins

A major contributor to aging and ARDs, such as AD [191] and PD [192], is oxidative stress induced by free radicals. Oxidative stress can directly activate glial cells, mainly by priming astrocytes, resulting in their interaction with neurons and the 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 [193].

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 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) [194]. Overall, AAC exhibits notable nootropic properties [195] and has been shown to decrease acetylcholinesterase activity in mice [107]. In addition, it facilitates the differentiation of neuronal and astrocyte precursors, thereby promoting synaptic maturation [196]. AAC is also essential for the biosynthesis of catecholamines, peptide amination, myelin formation, and the enhancement of synaptic function, while providing neuroprotection against glutamate toxicity [197,198].

In PD, dopamine metabolism generates oxidative stress products that contribute to accumulating abnormal proteins that are characteristic of PD [199]. 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 in vitro and animal models [108,109], more recent investigations have yielded inconsistent results [200]. Notably, AAC levels are lower in the substantia nigra compared to other brain regions [201,202], heightening its vulnerability to oxidative stress [203]. 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 h [204]. 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 [205,206]. 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 E12 rat mesencephalon [207]. 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 [208], although some studies have not corroborated these findings [209,210].

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 [114] and reduce ROS levels in Drosophila models [109]. Additional evidence underscoring the role of oxidative stress in PD includes observations that cellular antioxidants such as glutathione (GSH) are depleted in PD [211].

Specific isoforms of vitamin E, such as γ-tocotrienol and δ-tocotrienol, exert neuroprotective effects through the ERβ-PI3K/Akt signaling pathways in SH-SY5Y cells [115]. 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 [116]. 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 [212]. Perry et al. [117] similarly reported that mice treated with daily subcutaneous injections of high-dose α-tocopherol (αT) (2350 mg/kg body weight) 48 h before and 72 h 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 [118].

Conversely, L-AAC has also garnered attention for its beneficial effects on AD [213]. The primary neuroprotective mechanisms attributed to AAC include ROS-scavenging activity, neuroinflammation modulation, Aβ fibrillation inhibition, and the chelation of metals such as iron, copper, and zinc [214]. Furthermore, AAC has been shown to protect SH-SY5Y neuroblastoma cells from Aβ-mediated apoptosis [110] and, when administered orally, to reduce oxidative stress and neuroinflammation induced by Aβ fibrils in rats [111].

In contrast, vitamin E is a potent antioxidant that scavenges free radicals primarily through a hydrogen atom transfer mechanism [215]. Vitamin E plays a crucial role in the brain, is one of the most potent antioxidants, and has shown significant benefits in AD [216]. It counteracts Aβ-induced oxidative stress [119]; for instance, vitamin E has been demonstrated to prevent $A\beta_{1\text{-}42}$-induced protein oxidation, ROS production, and neurotoxicity in primary rat embryonic hippocampal neuronal cultures [119]. Moreover, although $A\beta_{1\text{-}42}$ 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 [217]. Vitamin E also helps preserve calcium homeostasis and protects against damage from Aβ deposits near cell membranes [218]. Additionally, it can

inhibit neuroinflammation by suppressing the production of prostaglandins E_2 and D_2, along with reducing cyclooxygenase and lipoxygenase activity [120,121].

Numerous research studies demonstrate that AAC and vitamin E can reduce cell senescence. However, limited evidence directly links cellular senescence, neurodegenerative diseases, and antioxidant vitamins. Most research has concentrated on other cell types, and only a few studies have investigated the potential role of antioxidant vitamins in influencing senescence and its related pathways in brain cells.

We highlight some relevant findings to offer a broader perspective on the capacity of antioxidant vitamins to modulate cellular senescence. Specifically, AAC downregulates SA-β-Gal and cell-cycle inhibitors (p53, p21, p16, and pRb) while upregulating activators (E2F1/2), reducing senescence in human dermal fibroblasts, hairless mice models, and LPS-treated human apical papilla cells [112,113].

Limited studies are also available regarding vitamin E supplementation. Vitamin E, including its phosphorylated form αTP, reduces SA-β-Gal activity in human fibroblasts and endothelial cells, with greater efficacy observed in cells from aged donors [122,123]. Specifically, vitamin E reduces SA-β-Gal levels in cells from both young and aged donors when reaching replicative senescence. This effect is also observed in earlier fibroblast passages from older subjects, likely due to a phosphorylated form of vitamin E, α-tocopheryl phosphate (αTP), which occurs in aging caused by reduced conversion to αT [123].

In summary, 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.

In addition to the well-known antioxidant vitamins, several others exert indirect antioxidant effects that may offer potential benefits for AD and PD.

Vitamin A, primarily through its active metabolite all-trans-retinoic acid (RA), plays a critical role in the CNS and maintains higher brain functions in aging individuals [219]. Although not classified as a direct antioxidant, RA exhibits significant indirect antioxidant properties [220]. In vitro studies have shown that vitamin A and β-carotene can inhibit the oligomerization of $A\beta_{40\text{-}42}$ peptides [124]. Mechanistically, the activation of retinoic acid receptor alpha (RARα) increases the expression of ADAM10/α-secretase, an enzyme that mitigates amyloid burden by cleaving APP in a non-amyloidogenic pathway without affecting β- or γ-secretase activity, as demonstrated in mouse cortical neurons [125]. However, high concentrations of retinol exposure (10 μM for 24 h) in SH-SY5Y cells increased Aβ levels and reduced cell viability, suggesting hormetic behavior with dose-dependent cytotoxic effects [126]. With aging, retinoid signaling remains essential for brain homeostasis; however, senescence-associated impairments can diminish vitamin A signaling efficacy [221].

RA signaling is implicated in PD neurogenesis and the differentiation of striatal neurons. The disruption of RAR/RXR pathways, as observed in transgenic RXR−/− and/or RAR−/− mice, has been shown to impair synaptic plasticity in the hippocampus and other brain regions, highlighting the critical role of vitamin A signaling in PD pathophysiology [127,222].

Although structurally and functionally heterogeneous, the B-vitamin group encompasses key antioxidant defense and neuroprotection cofactors. Vitamins B9 and B12 are essential for one-carbon metabolism, a biochemical network crucial for DNA synthesis, epigenetic regulation, and redox balance [223]. One-carbon metabolism is often disrupted in AD, and vitamin B9 supplementation has been shown to restore metabolic balance and

enhance cognitive outcomes, as evidenced by improved Mini–Mental State Examination (MMSE) scores in patients receiving vitamin B9 and B12 [128,129].

Beyond cognitive effects, vitamin B9 has also been reported to exert anti-aging properties. In the senescence-accelerated mouse prone 8 (SAMP8) model and primary astrocyte cultures, vitamin B9 supplementation (0–40 μM) reduced age-associated apoptosis and mitigated telomere attrition in cortical regions [130]. This finding is particularly relevant given that telomere shortening, a hallmark of replicative senescence, is often driven by oxidative stress and inflammation.

Plasma B12 levels correlate positively with telomere length and mitochondrial DNA copy number, declining with cellular aging [224–226].

Furthermore, vitamin B12 deficiency has been associated with the induction of cellular senescence markers in astrocytes. Specifically, B12-deficient astrocytes exhibit increased SA-β-gal activity and the upregulation of cell-cycle inhibitors $p16^{INK4a}$ and $p21^{CIP1}$, indicating a senescent phenotype [131].

Although not classified as antioxidants, vitamins A, B9, and B12 exhibit promising neuroprotective and anti-senescent properties. Therefore, their inclusion in this context is warranted, as they may pave the way for future studies exploring novel micronutrient-based interventions targeting age-related neurodegeneration and cellular senescence.

4.2. Polyphenols, Terpenes, and Terpenoids

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 [227,228].

A growing body of research demonstrates that polyphenols can modulate cellular senescence in many research studies and models. For example, in vitro, the 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 [229]. 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-1β [230]. Recent studies by Bientinesi et al. revealed that quercetin can prevent doxorubicin-induced senescence in human fibroblasts [132,133]. 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 senescence-associated heterochromatin foci (SAHF), Lamin B1 loss, and NF-κB 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 [134].

Moreover, polyphenols can also modulate senescence through a hormetic mechanism, as shown for resveratrol and curcumin [56,57].

Curcumin is well known for its antioxidant properties, which are mediated through the Keap1/Nrf2/ARE pathway. It exhibits dual characteristics: at high concentrations, curcumin can be cytotoxic to mammalian cells, while at subtoxic levels, it activates adaptive stress responses. This protective effect is evidenced by its ability to guard against glucose oxidase-mediated toxicity in astrocytes and aged Tg2576 mice with advanced amyloid ac-

cumulation [148,149]. Interestingly, curcumin can paradoxically stimulate ROS production at higher concentrations.

Similarly, resveratrol displays dose-dependent effects. It activates the SIRT1 and AMPK pathways, which enhance mitochondrial function and promote autophagy at low doses. In contrast, higher doses of resveratrol have been observed to induce oxidative damage in both in vivo and in vitro AD models [139,231].

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 [232].

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 [138,233].

Ginkgo biloba extract, containing flavonoids, organic acids, proanthocyanidins, and terpenoids such as ginkgolides A, B, C, M, J, and bilobalide, 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 [136]. Notably, Ginkgo biloba extract inhibited monoamine oxidase B (MAO-B) in vitro, reducing dopaminergic neuron degeneration [136,137].

Resveratrol, a nonflavonoid polyphenol found in grapes and berries, has shown promise in mitigating oxidative stress in a rat model of PD [234,235] while enhancing the number of dopaminergic neurons at the synapses through MAO suppression, in addition to preventing glutamate release [236–238].

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 [140], and it also inhibits α-synuclein fibril elongation, reducing the cytotoxic effects of α-synuclein oligomers [141]. Furthermore, oleuropein activates redox-sensitive transcription factors such as Nrf2, which may enhance the intracellular antioxidant capacity and contribute to neuroprotection [239].

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 [240,241]. Polyphenols reinforce endogenous antioxidant defenses and attenuate protein oxidation [242]. By sequestering reactive oxygen and nitrogen species, these compounds prevent the formation of toxic Aβ oligomers and modulate tau-protein hyperphosphorylation, thereby impeding the development of neurofibrillary tangles (NFTs) [243]. Additionally, polyphenols may help preserve neuronal integrity by interacting with transcription factors such as CREB and NF-κB [244].

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 Aβ 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 Aβ plaque-associated inflammation and cognitive deficits in AD mice [135]. Meanwhile, in PD, direct evidence of the beneficial effects of D+Q has not been observed, even though some advantages have been shown in aging killifish [245].

Additionally, fisetin, a natural senolytic, has been shown to improve cognitive function in mouse models of AD and dementia [142]. Among the senolytics tested in multiple

preclinical studies and increasing clinical trials, fisetin and D+Q appear to be the most effective [246,247].

Animal studies further substantiate the neuroprotective potential of polyphenols. For instance, mice receiving pomegranate juice, rich in polyphenols, exhibited significant improvements in both cued and spatial learning tasks, along with reduced hippocampal plaque loads, including both soluble and fibrillar forms of Aβ, as well as lower soluble $A\beta_{1\text{-}42}$ levels [248]. Red wine polyphenols have been shown to interfere with Aβ oligomerization, thereby attenuating Aβ neuropathology and cognitive decline in Tg2576 mice [249]. Mori et al. [250] 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 Aβ peptide levels.

Similarly, grape-derived polyphenolics from Vitis vinifera grape seeds significantly inhibited Aβ aggregation in vitro and ameliorated cognitive deterioration in Tg2576 mice when administered orally [251].

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.

In addition to polyphenols, terpenes and terpenoids exhibit notable neuroprotective, antioxidant, and anti-inflammatory properties, which may play a role in their anti-senescence effects. Among these compounds, limonene has shown hormetic-like activity.

While high doses of limonene are toxic to the Mediterranean fruit fly (Ceratitis capitata), with lethal doses recorded at 39.74 nL per male and 75.51 nL per female, lower doses (3.47 nL per male and 12.26 nL per female) have been found to extend lifespan. This highlights its potential in modulating aging processes [143].

Similarly, Ginsenoside F1, a minor saponin derived from Panax ginseng leaves, has been reported to suppress the SASP in astrocytes exposed to D-galactose. This effect is mediated by inhibiting the p38MAPK-dependent NF-κB signaling pathway, suggesting a potential role in reducing astrocyte-driven inflammation in AD [144]. Additionally, ginsenosides from P. ginseng have shown inhibitory activity against BACE1 activity in vitro, an important enzyme involved in Aβ production [145]. Artemisinin, a sesquiterpene lactone extracted from Artemisia annua, has shown moderate inhibition of acetylcholinesterase (AChE) at 1 mg/mL in vitro, alongside its known anti-inflammatory properties [146].

Another promising compound is Astragaloside IV (AS-IV), an antioxidant saponin extracted from the traditional Chinese medicinal herb Astragalus membranaceus Bunge. AS-IV exerts anti-inflammatory, neuroprotective, and longevity-promoting effects. In both replicative senescence (long-term culture-induced) and premature senescence models induced by LPS or MPP+, AS-IV attenuated astrocyte senescence by reducing SA-β-Gal activity and p16 expression while restoring nuclear lamin B1 levels and suppressing SASP. In a PD mouse model, AS-IV also protected against dopaminergic neuron loss and behavioral impairments, effects associated with a reduced accumulation of senescent astrocytes in the substantia nigra pars compacta [147].

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, in vitro studies have shown that black pepper oil, which contains terpenoid compounds such as β-caryophyllene, limonene, β-pinene, and

sabinene, has reduced the percentage of doxorubicin-induced senescent cells in CHO-K1 and NIH-3T3 cells [252]. Furthermore, curcumin, the primary component of Curcuma longa, has demonstrated a capacity to mitigate age-related deterioration by counteracting oxidative stress [253], modulating inflammatory pathways [254,255], promoting telomere elongation and telomerase activity [150], and influencing key metabolic regulators such as AMPK [256,257] and SIRTs [258,259]. Similarly, coriander seeds, which are rich in phenolic acids, coumarins, flavonoids, carotenoids, tocopherols, fatty acids, and sterols, have shown potential in reducing oxidative stress and cellular senescence, as evidenced by the decreased expression of senescence markers SA-β-Gal and p21 in the cardiac [260] and brain tissues [261] 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 [262]. Its neuroprotective effects are attributed mainly to its potent antioxidant properties, surpassing conventional antioxidants such as vitamins C and E [263,264]. The ability of curcumin to donate hydrogen ions from its β-diketone moiety is believed to underlie its anti-ROS activity [265]. Notably, pre- or post-treatment administration of curcumin in 6-OHDA-lesioned rats reduced dopaminergic neuron loss [151], while MES cells treated with curcumin exhibited increased Cu-Zn superoxide dismutase expression and reduced intracellular ROS accumulation [152]. 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 [266].

Similarly, piperine, the principal bioactive component of Piper nigrum (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 [157]. Additionally, piperine reduced microglial activation, IL-1β 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 [267]. Combining quercetin and piperine improved MPTP-induced behavioral and neurochemical deficits while mitigating oxidative stress and inflammation in the striatum [268].

Emerging in vitro evidence further supports the beneficial role of cinnamon and its metabolites in PD. Cinnamaldehyde (10 μM) was shown to protect BE(2)-M17 human neuroblastoma cells from MPP+-induced toxicity by inhibiting autophagy [160]. Cinnamon extract (CEppt), with its main bioactive component cinnamaldehyde, has also shown protective effects against 6-OHDA-induced cytotoxicity by enhancing cell viability, reducing apoptosis, and decreasing ROS levels [161]. Furthermore, CEppt has been found to interfere with α-synuclein aggregation by stabilizing its soluble oligomeric form and promoting the disassembly of preformed aggregates [162].

In addition to their anti-inflammatory properties, these bioactive compounds exert antioxidative effects and inhibit acetylcholinesterase activity and Aβ aggregation in AD. Curcumin has demonstrated potent antioxidant activity in both in vitro and in vivo models [269–271]. Mechanistically, curcumin enhances the macrophage-mediated clearance of Aβ plaques [153], suppresses microglial proliferation [272], attenuates neuroinflammation by downregulating pro-inflammatory cytokines [273,274], and inhibits oxidative stress by preventing free radical formation and propagation [154,275]. Remarkably, in vitro studies suggest that curcumin reduces Aβ levels by modulating APP processing and downregulat-

ing BACE1 expression [155]. Additionally, curcumin exhibits a high binding affinity for Aβ aggregates, thereby preventing their formation both in vitro and in vivo [156].

In addition to Curcuma longa, Cinnamomum verum has demonstrated significant neuroprotective properties. Studies have shown that cinnamon has potent antioxidant effects, boosting the activity of endogenous antioxidant enzymes through various antioxidant biomolecules. These include cinnamic acid, which is widely reported, and some phenolic compounds, such as proanthocyanidins A and B and kaempferol [276,277], which also simultaneously exert anti-inflammatory effects [163,278]. Notably, CEppt effectively inhibits the formation of toxic Aβ oligomers and protects neuronal PC12 cells from Aβ-induced toxicity, eliminating tetrameric Aβ species in the brain. Moreover, oral administration of this extract in an aggressive AD transgenic mouse model significantly reduced 6 kDa Aβ oligomers, diminished plaque burden, and improved cognitive performance [164].

Piperine has been reported to exert neuroprotective effects [158]. In animal models, black pepper administration reduced cholinesterase activity and amyloid plaque formation in the brain [159]. Furthermore, piperine significantly attenuated lipid peroxidation and acetylcholinesterase activity while preserving neuronal density in adult male Wistar rats [158].

Similarly, cardamom oil treatment, constituted by 1,8-cineole, α-terpinyl acetate, limonene, linalyl acetate, and linalool, 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 Aβ expression in the hippocampus and cortex [165].

Overall, accumulating evidence suggests that spices such as Curcuma longa, 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 the 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 acid (SCFA) production, impacting brain function through the microbiota–gut–brain axis [279,280].

Shi et al. studied dietary fiber deficiency (FD) in mice, revealing alterations in hippocampal synaptic ultrastructure, the proteome, and microglial–neuroinflammation pathways, affecting cognition and dopamine cholinergic synapses [279].

Gut microbiome alterations have also been linked to PD, with decreased SCFAs, particularly butyrate, observed in PD patients [281]. Similarly, Matt et al. showed that butyrate administration and high-fiber diets reduced neuroinflammation in aged mice [166].

For AD, dietary fiber and SCFAs have shown benefits in cholesterol reduction, Aβ clearance, and neuroinflammation regulation, potentially mitigating Aβ deposition and brain hypometabolism [282–285].

Furthermore, in vitro studies found valeric, butyric, and propionic acids to interfere with neurotoxic Aβ aggregation [167], while in vivo, fiber influenced amyloid load in GPCR KO mice, suggesting a role in amyloid metabolism [168].

4.5. Probiotics and Prebiotics

Probiotics and prebiotics influence human health by modulating metabolic regulation, immune response, and neurological function via the gut microbiome [286–290].

Probiotics, particularly Lactobacilli species, have demonstrated benefits in aging by enhancing immunity and maintaining gut microbiota balance, potentially extending the healthspan [289,291–293]. Probiotics can regulate neuroinflammation and oxidative stress in neurodegenerative diseases, reducing the risk of disorders like PD and AD [169–171,294]. Furthermore, as previously mentioned, in synergy with polyphenols, probiotics can also function as hormetic nutrients modulating antioxidant and anti-inflammatory signaling pathways [54].

In PD, probiotics improve gut health, mitigate permeability, and reduce neuroinflammation [295]. Cellular studies show that probiotic treatment can shift cytokine production towards an anti-inflammatory profile [172], while in vivo studies suggest protection against dopaminergic neuron loss and neurotrophic factor depletion [173–175].

Similarly, specific probiotic strains in rat models can restore gut microbiota balance in AD, improve cognitive function, and mitigate pathological features such as Aβ deposition and oxidative stress [296,297]. However, the precise mechanisms remain unclear [176,177], 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 [298]. They modulate oxidative damage, enhance GLP-1 secretion, and potentially regulate brain glucose metabolism and CNS inflammation via GLP-1 receptors [299,300]. Prebiotics modulate gut microbiota composition in PD, reducing pro-inflammatory bacteria and increasing SCFA-producing taxa with promising neuroprotective effects [178,179]. Intriguingly, their combination with probiotics, via the consumption of fermented milk containing multiple probiotic strains and prebiotic fiber [301], appears particularly beneficial in PD patients, improving gut motility [301,302].

On the other hand, prebiotic supplementation in AD rodent models has shown improvements in neurotransmitter levels, cognitive function, and Aβ pathology, with chitosan oligosaccharides demonstrating neuroprotective properties in several studies [180].

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.

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 [303]. 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 [304].

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 [305,306]. 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 [307]. Inter-

estingly, 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 [308,309]. These fatty acids also possess antioxidant and anti-apoptotic effects, mitigating neurotoxicity in preclinical models [181,310].

Research on dietary fats is still emerging in PD, but observational studies suggest that LCPUFA intake may offer neuroprotection [182,311]. 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 [183]. Additionally, n-3 PUFAs have neuroprotective effects in MPTP-induced PD mice models, preventing neuronal loss and preserving striatal dopamine levels [181,184,312–314].

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 [185,309]. Other RCTs in individuals with mild-to-moderate AD have reported cognitive improvements following supplementation [186,315]. Animal studies suggest that DHA reduces amyloid accumulation, tau pathology, and synaptic dysfunction, with several independent reports confirming reduced Aβ levels in APP transgenic models following DHA-enriched diets [187–190,316].

5. Conclusions and Future Perspectives

This review highlights the important role of nutraceuticals and functional foods in reducing aging and neurodegenerative diseases by modulating cellular senescence and its related aspects. 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.

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

Even though this review highlights substantial evidence supporting the nutraceuticals' beneficial effects on cellular senescence 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 in 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, this review suggests that incorporating nutraceuticals into comprehensive dietary interventions may help reduce the risk of neurodegenerative diseases. However, the scarcity of clinical data raises questions about their effectiveness, especially considering the emerging hormetic properties of specific nutraceuticals. Last but not least is the issue of the doses to be used in vivo to achieve an effect, considering aspects of absorption, interactions, therapies, and individual characteristics that could influence functionality. 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.

Future research should overcome the current translational gap by prioritizing mechanistic studies utilizing transcriptomics, proteomics, and metabolomics to elucidate whether nutraceuticals exhibit senomorphic or senolytic properties and affect the corresponding pathways involved. Experimental models mimicking the brain's cellular complexity, such as co-cultures and 3D organoids, should be employed to better capture the pathophysiology and the impact of nutraceuticals on brain senescence and neuroinflammation. In vivo studies using animal models of Alzheimer's and Parkinson's diseases are also necessary to evaluate senescence biomarkers, including pro-inflammatory cytokines, genetic markers, and cognitive outcomes.

Identifying characteristic proteins associated with senescence-related phenotypes and cataloguing potential senescence biomarkers is imperative. This work will aid in evaluating the burden of senescence, the stimuli that trigger this process, and the tissue origins of senescent cells in vivo. Such information could prove invaluable in assessing the therapeutic benefits of nutraceuticals in living organisms.

Moreover, enhancing the bioavailability of nutraceuticals through novel delivery systems and investigating their effects within comprehensive dietary contexts, such as the Mediterranean diet (MedDiet), will increase their translational potential. Clinically, pilot trials in frail or cognitively impaired older adults, supported by validated senescence biomarkers, could provide early insights into efficacy. Lastly, integration with genetic and epigenetic studies should be pursued to assess individual responses to nutraceuticals and develop highly personalized functional foods tailored to specific diet patterns.

6. Limitations

This review provides a comprehensive overview of the current literature on the role of nutraceuticals and functional foods in modulating cellular senescence and their potential implications for neurodegenerative diseases. Nonetheless, several limitations warrant consideration. Most available evidence stems from in vitro or animal studies, with limited clinical validation. Despite promising preclinical data, the clinical utility remains uncertain due to poor bioavailability, a short half-life, and inter-individual variability, which restricts translational relevance. Additionally, hormetic effects add a layer of complexity, as beneficial effects depend on dose optimization, a factor rarely addressed. Indeed, an additional challenge lies in determining effective in vivo dosing, since absorption, metabolism, and tissue distribution rarely correlate linearly with the administered dose. Additionally, age-related changes, causing reduced renal and hepatic clearance, an increased volume of distribution for lipophilic drugs, and prolonged elimination half-life, alongside heightened pharmacodynamic sensitivity, further complicate dose selection [317]. As a result, dosing must consider the target medical condition, patient-specific factors, and health status. The safety profiles of the reviewed molecules in humans are primarily still being defined. However, a safe dosage in humans has been gauged for some natural compounds, such as resveratrol (500 mg) [318], Ginkgo Biloba extract (120 mg) [319], and curcumin (1–6 g a day for 4–7 weeks) [320]. Some compounds discussed in this review exert pleiotropic effects on multiple biological pathways, challenging the attribution of their benefits to senescence-related mechanisms. Variability in compound purity, bioavailability, and dosing further complicates comparisons across studies in terms of robustness and significance. Collectively, these factors highlight the need for more rigorous, standardized, and clinically focused research.

Author Contributions: Conceptualization, S.R., G.B., E.B. and D.M.; writing—original draft preparation, S.R. and 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 has been co-funded by Next Generation EU, in the context of the National Recovery and Resilience Plan, Investment Partenariato Esteso PE8 -Project Age-IT: "Ageing Well in an Ageing Society" to D.M. 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

References

1. World Health Organization. *World Population Prospects 2022*; WHO: Geneva, Switzerland, 2022; ISBN 978-92-1-148373-4.
2. Santana, P.; Grant, M. *Global Aging and Health Determinants in a Changing World*; INC: New York, NY, USA, 2023; ISBN 9780128237618.
3. World Health Organization. *World Population Ageing 2019*; World Health Organization: Geneva, Switzerland, 2019; ISBN 9789211483260.
4. Nemitz, J. Increasing Longevity and Life Satisfaction: Is There a Catch to Living Longer? *J. Popul. Econ.* **2022**, *35*, 557–589. [CrossRef]

5. Olshansky, S.J. From Lifespan to Healthspan. *JAMA* **2018**, *320*, 1323. [CrossRef] [PubMed]
6. Garmany, A.; Yamada, S.; Terzic, A. Longevity Leap: Mind the Healthspan Gap. *NPJ Regen. Med.* **2021**, *6*, 57. [CrossRef] [PubMed]
7. Ostan, R.; Bucci, L.; Capri, M.; Salvioli, S.; Scurti, M.; Pini, E.; Monti, D.; Franceschi, C. Immunosenescence and Immunogenetics of Human Longevity. *Neuroimmunomodulation* **2008**, *15*, 224–240. [CrossRef]
8. Cevenini, E.; Bellavista, E.; Tieri, P.; Castellani, G.; Lescai, F.; Francesconi, M.; Mishto, M.; Santoro, A.; Valensin, S.; Salvioli, S.; et al. Systems Biology and Longevity: An Emerging Approach to Identify Innovative Anti-Aging Targets and Strategies. *Curr. Pharm. Des.* **2010**, *16*, 802–813. [CrossRef]
9. Li, X.; Li, C.; Zhang, W.; Wang, Y.; Qian, P.; Huang, H. Inflammation and Aging: Signaling Pathways and Intervention Therapies. *Signal Transduct. Target. Ther.* **2023**, *8*, 239. [CrossRef]
10. Franceschi, C.; Bonafè, M.; Valensin, S.; Olivieri, F.; De Luca, M.; Ottaviani, E.; De Benedictis, G. Inflamm-Aging. An Evolutionary Perspective on Immunosenescence. *Ann. N. Y. Acad. Sci.* **2000**, *908*, 244–254. [CrossRef]
11. Franceschi, C.; Capri, M.; Monti, D.; Giunta, S.; Olivieri, F.; Sevini, F.; Panourgia, M.P.; Invidia, L.; Celani, L.; Scurti, M.; et al. Inflammaging and Anti-Inflammaging: A Systemic Perspective on Aging and Longevity Emerged from Studies in Humans. *Mech. Ageing Dev.* **2007**, *128*, 92–105. [CrossRef]
12. López-Otín, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. Hallmarks of Aging: An Expanding Universe. *Cell* **2023**, *186*, 243–278. [CrossRef]
13. Franceschi, C.; Garagnani, P.; Morsiani, C.; Conte, M.; Santoro, A.; Grignolio, A.; Monti, D.; Capri, M.; Salvioli, S. The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates. *Front. Med.* **2018**, *5*, 61. [CrossRef]
14. Sierra, F.; Kohanski, R. Geroscience and the Trans-NIH Geroscience Interest Group, GSIG. *Geroscience* **2017**, *39*, 1–5. [CrossRef] [PubMed]
15. Mattson, M.P. Hormesis Defined. *Ageing Res. Rev.* **2008**, *7*, 1–7. [CrossRef] [PubMed]
16. Rattan, S.I.S. Hormesis in Aging. *Ageing Res. Rev.* **2008**, *7*, 63–78. [CrossRef]
17. Sharma, V.; Mehdi, M.M. Oxidative Stress, Inflammation and Hormesis: The Role of Dietary and Lifestyle Modifications on Aging. *Neurochem. Int.* **2023**, *164*, 105490. [CrossRef]
18. Prattichizzo, F.; Frigé, C.; Pellegrini, V.; Scisciola, L.; Santoro, A.; Monti, D.; Rippo, M.R.; Ivanchenko, M.; Olivieri, F.; Franceschi, C. Organ-Specific Biological Clocks: Ageotyping for Personalized Anti-Aging Medicine. *Ageing Res. Rev.* **2024**, *96*, 102253. [CrossRef]
19. Fjell, A.M.; Walhovd, K.B. Structural Brain Changes in Aging: Courses, Causes and Cognitive Consequences. *Rev. Neurosci.* **2010**, *21*, 187–221. [CrossRef]
20. Rodrigue, K.M.; Kennedy, K.M. The Cognitive Consequences of Structural Changes to the Aging Brain, 7th ed.Elsevier Inc.: Amsterdam, The Netherlands, 2011; ISBN 9780123808820.
21. Nyberg, L.; Wåhlin, A. The Many Facets of Brain Aging. *Elife* **2020**, *9*, 18–20. [CrossRef]
22. Murman, D.L. The Impact of Age on Cognition. *Semin. Hear.* **2015**, *36*, 111–121. [CrossRef]
23. Fjell, A.M.; Sneve, M.H.; Grydeland, H.; Storsve, A.B.; Amlien, I.K.; Yendiki, A.; Walhovd, K.B. Relationship between Structural and Functional Connectivity Change across the Adult Lifespan: A Longitudinal Investigation. *Hum. Brain Mapp.* **2017**, *38*, 561–573. [CrossRef]
24. Seidler, R.D.; Bernard, J.A.; Burutolu, T.B.; Fling, B.W.; Gordon, M.T.; Gwin, J.T.; Kwak, Y.; Lipps, D.B. Motor Control and Aging: Links to Age-Related Brain Structural, Functional, and Biochemical Effects. *Neurosci. Biobehav. Rev.* **2010**, *34*, 721–733. [CrossRef]
25. Park, D.C.; Reuter-Lorenz, P. The Adaptive Brain: Aging and Neurocognitive Scaffolding. *Annu. Rev. Psychol.* **2009**, *60*, 173–196. [CrossRef] [PubMed]
26. Zhang, Q.; Yang, G.; Luo, Y.; Jiang, L.; Chi, H.; Tian, G. Neuroinflammation in Alzheimer's Disease: Insights from Peripheral Immune Cells. *Immun. Ageing* **2024**, *21*, 38. [CrossRef] [PubMed]
27. Kumari, R.; Jat, P. Mechanisms of Cellular Senescence: Cell Cycle Arrest and Senescence Associated Secretory Phenotype. *Front. Cell Dev. Biol.* **2021**, *9*, 645593. [CrossRef] [PubMed]
28. Hayflick, L. The Limited in vitro Lifetime of Human Diploid Cell Strains. *Exp. Cell Res.* **1965**, *37*, 614–636. [CrossRef]
29. Campisi, J.; D'Adda Di Fagagna, F. Cellular Senescence: When Bad Things Happen to Good Cells. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 729–740. [CrossRef]
30. González-Gualda, E.; Baker, A.G.; Fruk, L.; Muñoz-Espín, D. A Guide to Assessing Cellular Senescence in vitro and in vivo. *FEBS J.* **2021**, *288*, 56–80. [CrossRef]
31. Campisi, J. Aging, Cellular Senescence, and Cancer. *Annu. Rev. Physiol.* **2013**, *75*, 685–705. [CrossRef]
32. Idda, M.L.; McClusky, W.G.; Lodde, V.; Munk, R.; Abdelmohsen, K.; Rossi, M.; Gorospe, M. Survey of Senescent Cell Markers with Age in Human Tissues. *Aging* **2020**, *12*, 4052–4066. [CrossRef]
33. Krishnamurthy, J.; Torrice, C.; Ramsey, M.R.; Kovalev, G.I.; Al-Regaiey, K.; Su, L.; Sharpless, N.E. Ink4a/Arf Expression Is a Biomarker of Aging. *J. Clin. Investig.* **2004**, *114*, 1299–1307. [CrossRef]
34. Yousefzadeh, M.J.; Wilkinson, J.E.; Hughes, B.; Gadela, N.; Ladiges, W.C.; Vo, N.; Niedernhofer, L.J.; Huffman, D.M.; Robbins, P.D. Heterochronic Parabiosis Regulates the Extent of Cellular Senescence in Multiple Tissues. *Geroscience* **2020**, *42*, 951–961. [CrossRef]

35. Si, Z.; Sun, L.; Wang, X. Evidence and Perspectives of Cell Senescence in Neurodegenerative Diseases. *Biomed. Pharmacother.* **2021**, *137*, 111327. [CrossRef] [PubMed]
36. Boyko, A.A.; Troyanova, N.I.; Kovalenko, E.I.; Sapozhnikov, A.M. Similarity and Differences in Inflammation-Related Characteristics of the Peripheral Immune System of Patients with Parkinson's and Alzheimer's Diseases. *Int. J. Mol. Sci.* **2017**, *18*, 2633. [CrossRef] [PubMed]
37. Nakajima, K.; Kohsaka, S. Microglia: Neuroprotective and Neurotrophic Cells in the Central Nervous System. *Curr. Drug Targets Cardiovasc. Haematol. Disord.* **2004**, *4*, 65–84. [CrossRef]
38. Diwan, B.; Sharma, R. Nutritional Components as Mitigators of Cellular Senescence in Organismal Aging: A Comprehensive Review. *Food Sci. Biotechnol.* **2022**, *31*, 1089–1109. [CrossRef]
39. Głowacka, P.; Oszajca, K.; Pudlarz, A.; Szemraj, J.; Witusik-Perkowska, M. Postbiotics as Molecules Targeting Cellular Events of Aging Brain—The Role in Pathogenesis, Prophylaxis and Treatment of Neurodegenerative Diseases. *Nutrients* **2024**, *16*, 2244. [CrossRef]
40. Bhat, R.; Crowe, E.P.; Bitto, A.; Moh, M.; Katsetos, C.D.; Garcia, F.U.; Johnson, F.B.; Trojanowski, J.Q.; Sell, C.; Torres, C. Astrocyte Senescence as a Component of Alzheimer's Disease. *PLoS ONE* **2012**, *7*, e45069. [CrossRef]
41. Walker, L.; Jacobs, E.; McAleese, K.E.; Johnson, M.; Attems, J. Do Senescent Cells Play a Role in Alzheimer's Disease? *Alzheimer's Dement.* **2020**, *16*, 43820. [CrossRef]
42. Simmnacher, K.; Krach, F.; Schneider, Y.; Alecu, J.E.; Mautner, L.; Klein, P.; Roybon, L.; Prots, I.; Xiang, W.; Winner, B. Unique Signatures of Stress-Induced Senescent Human Astrocytes. *Exp. Neurol.* **2020**, *334*, 113466. [CrossRef]
43. Chinta, S.J.; Woods, G.; Demaria, M.; Rane, A.; Zou, Y.; McQuade, A.; Rajagopalan, S.; Limbad, C.; Madden, D.T.; Campisi, J.; et al. Cellular Senescence Is Induced by the Environmental Neurotoxin Paraquat and Contributes to Neuropathology Linked to Parkinson's Disease. *Cell Rep.* **2018**, *22*, 930–940. [CrossRef]
44. Wang, W.Y.; Tan, M.S.; Yu, J.T.; Tan, L. Role of Pro-Inflammatory Cytokines Released from Microglia in Alzheimer's Disease. *Ann. Transl. Med.* **2015**, *3*, 136. [CrossRef]
45. Hou, Y.; Wei, Y.; Lautrup, S.; Yang, B.; Wang, Y.; Cordonnier, S.; Mattson, M.P.; Croteau, D.L.; Bohr, V.A. NAD+ Supplementation Reduces Neuroinflammation and Cell Senescence in a Transgenic Mouse Model of Alzheimer's Disease via CGAS-STING. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2011226118. [CrossRef] [PubMed]
46. Dehkordi, S.K.; Walker, J.; Sah, E.; Bennett, E.; Atrian, F.; Frost, B.; Woost, B.; Bennett, R.E.; Orr, T.C.; Zhou, Y.; et al. Profiling Senescent Cells in Human Brains Reveals Neurons with CDKN2D/P19 and Tau Neuropathology. *Nat. Aging* **2021**, *1*, 1107–1116. [CrossRef] [PubMed]
47. Bussian, T.; Aziz, A.; Meyer, C.; Swenson, B.; Deursen, J.; Baker, D. Clearance of Senescent Glial Cells Prevents Tau-Dependent Pathology and Cognitive Decline. *Nature* **2018**, *562*, 578–582. [CrossRef] [PubMed]
48. López-Otín, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The Hallmarks of Aging. *Cell* **2013**, *153*, 1194–1217. [CrossRef]
49. Mathers, J.C. Impact of Nutrition on the Ageing Process. *Br. J. Nutr.* **2015**, *113*, S18–S22. [CrossRef]
50. Biesalski, H.K.; Dragsted, L.O.; Elmadfa, I.; Grossklaus, R.; Müller, M.; Schrenk, D.; Walter, P.; Weber, P. Bioactive Compounds: Definition and Assessment of Activity. *Nutrition* **2009**, *25*, 1202–1205. [CrossRef]
51. Morris, M.C. Nutrition and Risk of Dementia: Overview and Methodological Issues. *Ann. N. Y. Acad. Sci.* **2016**, *1367*, 31–37. [CrossRef]
52. Hayes, D.P. Nutritional Hormesis. *Eur. J. Clin. Nutr.* **2007**, *61*, 147–159. [CrossRef]
53. Scuto, M.C.; Mancuso, C.; Tomasello, B.; Ontario, M.L.; Cavallaro, A.; Frasca, F.; Maiolino, L.; Salinaro, A.T.; Calabrese, E.J.; Calabrese, V. Curcumin, Hormesis and the Nervous System. *Nutrients* **2019**, *11*, 2417. [CrossRef]
54. Scuto, M.; Rampulla, F.; Reali, G.M.; Spanò, S.M.; Trovato Salinaro, A.; Calabrese, V. Hormetic Nutrition and Redox Regulation in Gut–Brain Axis Disorders. *Antioxidants* **2024**, *13*, 484. [CrossRef]
55. Santoro, A.; Martucci, M.; Conte, M.; Capri, M.; Franceschi, C.; Salvioli, S. Inflammaging, Hormesis and the Rationale for Anti-Aging Strategies. *Ageing Res. Rev.* **2020**, *64*, 101142. [CrossRef] [PubMed]
56. Bucciantini, M.; Leri, M.; Scuto, M.; Ontario, M.; Trovato Salinaro, A.; Calabrese, E.J.; Calabrese, V.; Stefani, M. Xenohormesis Underlyes the Anti-Aging and Healthy Properties of Olive Polyphenols. *Mech. Ageing Dev.* **2022**, *202*, 111620. [CrossRef] [PubMed]
57. Calabrese, V.; Cornelius, C.; Dinkova-Kostova, A.T.; Calabrese, E.J.; Mattson, M.P. Cellular Stress Responses, The Hormesis Paradigm, and Vitagenes: Novel Targets for Therapeutic Intervention in Neurodegenerative Disorders. *Antioxid. Redox Signal.* **2010**, *13*, 1763–1811. [CrossRef]
58. Aliper, A.; Belikov, A.V.; Garazha, A.; Jellen, L.; Artemov, A.; Suntsova, M.; Ivanova, A.; Venkova, L.; Borisov, N.; Buzdin, A.; et al. In Search for Geroprotectors: In Silico Screening and in vitro Validation of Signalome-Level Mimetics of Young Healthy State. *Aging* **2016**, *8*, 2127–2152. [CrossRef]
59. Aliper, A.; Jellen, L.; Cortese, F.; Artemov, A.; Semper, D.K.; Moskalev, A.; Swick, A.G.; Zhavoronkov, A. Natural Mimetics of Rapamycin and Minoxidil Obtained via Computational Methods. *Aging* **2017**, *9*, 2245–2268. [CrossRef]

60. Wang, Z.; Zhang, L.; Liang, Y.; Zhang, C.; Xu, Z.; Zhang, L.; Fuji, R.; Mu, W.; Li, L.; Jiang, J.; et al. Cyclic AMP Mimics the Anti-Ageing Effects of Calorie Restriction by Up-Regulating Sirtuin. *Sci. Rep.* **2015**, *5*, 12012. [CrossRef]
61. Naisam, S.; Mohan, A.; Sreekumar, N. Epigenetic Regulation of Human Sirtuin 1 Insights into Aging Mechanisms. *Preprint* **2024**. [CrossRef]
62. Penantian, R.M.; Antarianto, R.D.; Hardiany, N.S. Effect of Calorie Restriction on the Expression of Sirtuin1 as an Antiaging Biomarker. *Makara J. Sci.* **2023**, *27*, 3. [CrossRef]
63. Dhillon, R.S.; Qin, Y.; van Ginkel, P.R.; Fu, V.X.; Vann, J.M.; Lawton, A.J.; Green, C.L.; Manchado-Gobatto, F.B.; Gobatto, C.A.; Lamming, D.W.; et al. SIRT3 Deficiency Decreases Oxidative Metabolism Capacity but Increases Lifespan in Male Mice under Caloric Restriction. *Aging Cell* **2022**, *21*, e13721. [CrossRef]
64. Gurău, F.; Baldoni, S.; Prattichizzo, F.; Espinosa, E.; Amenta, F.; Procopio, A.D.; Albertini, M.C.; Bonafè, M.; Olivieri, F. Anti-Senescence Compounds: A Potential Nutraceutical Approach to Healthy Aging. *Ageing Res. Rev.* **2018**, *46*, 14–31. [CrossRef]
65. Hadem, I.K.H.; Majaw, T.; Kharbuli, B.; Sharma, R. Beneficial Effects of Dietary Restriction in Aging Brain. *J. Chem. Neuroanat.* **2019**, *95*, 123–133. [CrossRef] [PubMed]
66. Fontana, L.; Mitchell, S.E.; Wang, B.; Tosti, V.; van Vliet, T.; Veronese, N.; Bertozzi, B.; Early, D.S.; Maissan, P.; Speakman, J.R.; et al. The Effects of Graded Caloric Restriction: XII. Comparison of Mouse to Human Impact on Cellular Senescence in the Colon. *Aging Cell* **2018**, *17*, 4–8. [CrossRef] [PubMed]
67. Wang, C.; Maddick, M.; Miwa, S.; Jurk, D.; Czapiewski, R.; Saretzki, G.; Langie, S.A.S.; Godschalk, R.W.L.; Cameron, K.; von Zglinicki, T. Adult-Onset, Short-Term Dietary Restriction Reduces Cell Senescence in Mice. *Aging* **2010**, *2*, 555–566. [CrossRef]
68. Aversa, Z.; White, T.A.; Heeren, A.A.; Hulshizer, C.A.; Saul, D.; Zhang, X.; Molina, A.J.A.; Redman, L.M.; Martin, C.K.; Racette, S.B.; et al. Calorie Restriction Reduces Biomarkers of Cellular Senescence in Humans. *Aging Cell* **2024**, *23*, e14038. [CrossRef]
69. Forni, C.; Facchiano, F.; Bartoli, M.; Pieretti, S.; Facchiano, A.; D'Arcangelo, D.; Norelli, S.; Valle, G.; Nisini, R.; Beninati, S.; et al. Beneficial Role of Phytochemicals on Oxidative Stress and Age-Related Diseases. *Biomed. Res. Int.* **2019**, *2019*, 8748253. [CrossRef]
70. Ooi, T.C.; Meramat, A.; Rajab, N.F.; Shahar, S.; Ismail, I.S.; Azam, A.A.; Sharif, R. Intermittent Fasting Enhanced the Cognitive Function in Older Adults with Mild Cognitive Impairment by Inducing Biochemical and Metabolic Changes: A 3-Year Progressive Study. *Nutrients* **2020**, *12*, 2644. [CrossRef]
71. Teng, N.I.M.F.; Shahar, S.; Rajab, N.F.; Manaf, Z.A.; Johari, M.H.; Ngah, W.Z.W. Improvement of Metabolic Parameters in Healthy Older Adult Men Following a Fasting Calorie Restriction Intervention. *Aging Male* **2013**, *16*, 177–183. [CrossRef]
72. Chiavaroli, L.; Nishi, S.K.; Khan, T.A.; Braunstein, C.R.; Glenn, A.J.; Mejia, S.B.; Rahelić, D.; Kahleová, H.; Salas-Salvadó, J.; Jenkins, D.J.A.; et al. Portfolio Dietary Pattern and Cardiovascular Disease: A Systematic Review and Meta-Analysis of Controlled Trials. *Prog. Cardiovasc. Dis.* **2018**, *61*, 43–53. [CrossRef]
73. Ndanuko, R.N.; Tapsell, L.C.; Charlton, K.E.; Neale, E.P.; Batterham, M.J. Dietary Patterns and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Adv. Nutr.* **2016**, *7*, 76–89. [CrossRef]
74. Barbaresko, J.; Koch, M.; Schulze, M.B.; Nöthlings, U. Dietary Pattern Analysis and Biomarkers of Low-Grade Inflammation: A Systematic Literature Review. *Nutr. Rev.* **2013**, *71*, 511–527. [CrossRef]
75. Grande de França, N.A.; Rolland, Y.; Guyonnet, S.; de Souto Barreto, P. The Role of Dietary Strategies in the Modulation of Hallmarks of Aging. *Ageing Res. Rev.* **2023**, *87*, 101908. [CrossRef]
76. Ravussin, E.; Redman, L.M.; Rochon, J.; Das, S.K.; Fontana, L.; Kraus, W.E.; Romashkan, S.; Williamson, D.A.; Meydani, S.N.; Villareal, D.T.; et al. A 2-Year Randomized Controlled Trial of Human Caloric Restriction: Feasibility and Effects on Predictors of Health Span and Longevity. *J. Gerontol. A Biol. Sci. Med. Sci.* **2015**, *70*, 1097–1104. [CrossRef] [PubMed]
77. Panda, S.; Maier, G.; Villareal, D.T. Targeting Energy Intake and Circadian Biology to Engage Mechanisms of Aging in Older Adults with Obesity: Calorie Restriction and Time-Restricted Eating. *J. Gerontol. Ser. A* **2023**, *78*, 79–85. [CrossRef] [PubMed]
78. Alì, S.; Davinelli, S.; Accardi, G.; Aiello, A.; Caruso, C.; Duro, G.; Ligotti, M.E.; Pojero, F.; Scapagnini, G.; Candore, G. Healthy Ageing and Mediterranean Diet: A Focus on Hormetic Phytochemicals. *Mech. Ageing Dev.* **2021**, *200*, 111592. [CrossRef] [PubMed]
79. Masoro, E.J. Role of Hormesis in Life Extension by Caloric Restriction. *Dose-Response* **2007**, *5*, 163–173. [CrossRef]
80. Sofi, F.; Cesari, F.; Abbate, R.; Gensini, G.F.; Casini, A. Adherence to Mediterranean Diet and Health Status: Meta-Analysis. *BMJ* **2008**, *337*, a1344. [CrossRef]
81. Xavier Medina, F. Mediterranean Diet, Culture and Heritage: Challenges for a New Conception. *Public Health Nutr.* **2009**, *12*, 1618–1620. [CrossRef]
82. Marin, C.; Delgado-Lista, J.; Ramirez, R.; Carracedo, J.; Caballero, J.; Perez-Martinez, P.; Gutierrez-Mariscal, F.M.; Garcia-Rios, A.; Delgado-Casado, N.; Cruz-Teno, C.; et al. Mediterranean Diet Reduces Senescence-Associated Stress in Endothelial Cells. *Age* **2012**, *34*, 1309–1316. [CrossRef]
83. Salas-Salvadó, J.; Guasch-Ferré, M.; Lee, C.H.; Estruch, R.; Clish, C.B.; Ros, E. Protective Effects of the Mediterranean Diet on Type 2 Diabetes and Metabolic Syndrome. *J. Nutr.* **2016**, *146*, 920S–927S. [CrossRef]

84. Wade, A.T.; Davis, C.R.; Dyer, K.A.; Hodgson, J.M.; Woodman, R.J.; Keage, H.A.D.; Murphy, K.J. A Mediterranean Diet to Improve Cardiovascular and Cognitive Health: Protocol for a Randomised Controlled Intervention Study. *Nutrients* **2017**, *9*, 145. [CrossRef]
85. Fekete, M.; Varga, P.; Ungvari, Z.; Tibor, J.; Annamaria, F.; Ágnes, B.; Lehoczki, A.; Mózes, N.; Grosso, G.; Godos, J.; et al. The Role of the Mediterranean Diet in Reducing the Risk of Cognitive Impairement, Dementia, and Alzheimer ' s Disease: A Meta—Analysis. *Geroscience* **2025**. *ahead of print*. [CrossRef]
86. Andreo-López, M.C.; Contreras-Bolívar, V.; Muñoz-Torres, M.; García-Fontana, B.; García-Fontana, C. Influence of the Mediterranean Diet on Healthy Aging. *Int. J. Mol. Sci.* **2023**, *24*, 4491. [CrossRef] [PubMed]
87. Marin, C.; Ramirez, R.; Delgado-Lista, J.; Yubero-Serrano, E.M.; Perez-Martinez, P.; Carracedo, J.; Garcia-Rios, A.; Rodriguez, F.; Gutierrez-Mariscal, F.M.; Gomez, P.; et al. Mediterranean Diet Reduces Endothelial Damage and Improves the Regenerative Capacity of Endothelium. *Am. J. Clin. Nutr.* **2011**, *93*, 267–274. [CrossRef]
88. Mantilla-Escalante, D.C.; López de las Hazas, M.C.; Crespo, M.C.; Martín-Hernández, R.; Tomé-Carneiro, J.; del Pozo-Acebo, L.; Salas-Salvadó, J.; Bulló, M.; Dávalos, A. Mediterranean Diet Enriched in Extra-Virgin Olive Oil or Nuts Modulates Circulating Exosomal Non-Coding RNAs. *Eur. J. Nutr.* **2021**, *60*, 4279–4293. [CrossRef]
89. Bacalini, M.G.; Friso, S.; Olivieri, F.; Pirazzini, C.; Giuliani, C.; Capri, M.; Santoro, A.; Franceschi, C.; Garagnani, P. Present and Future of Anti-Ageing Epigenetic Diets. *Mech. Ageing Dev.* **2014**, *136–137*, 101–115. [CrossRef]
90. Lee, P.S.; Chiou, Y.S.; Ho, C.T.; Pan, M.H. Chemoprevention by Resveratrol and Pterostilbene: Targeting on Epigenetic Regulation. *BioFactors* **2018**, *44*, 26–35. [CrossRef]
91. Bekdash, R.A. Epigenetics, Nutrition, and the Brain: Improving Mental Health through Diet. *Int. J. Mol. Sci.* **2024**, *25*, 4036. [CrossRef]
92. Pazoki-Toroudi, H.; Amani, H.; Ajami, M.; Nabavi, S.F.; Braidy, N.; Kasi, P.D.; Nabavi, S.M. Targeting MTOR Signaling by Polyphenols: A New Therapeutic Target for Ageing. *Ageing Res. Rev.* **2016**, *31*, 55–66. [CrossRef]
93. Gillette-Guyonnet, S.; Secher, M.; Vellas, B. Nutrition and Neurodegeneration: Epidemiological Evidence and Challenges for Future Research. *Br. J. Clin. Pharmacol.* **2013**, *75*, 738–755. [CrossRef]
94. Vellas, B.; Carrie, I.; Gillette-Guyonnet, S.; Touchon, J.; Dantoine, T.; Dartigues, J.F.; Cuffi, M.N.; Bordes, S.; Gasnier, Y.; Robert, P.; et al. Alzheimer's Disease: Design and Baseline Data. *J. Prev. Alzheimer's Dis.* **2014**, *1*, 13–22.
95. Ngandu, T.; Lehtisalo, J.; Solomon, A.; Levälahti, E.; Ahtiluoto, S.; Antikainen, R.; Bäckman, L.; Hänninen, T.; Jula, A.; Laatikainen, T.; et al. A 2 Year Multidomain Intervention of Diet, Exercise, Cognitive Training, and Vascular Risk Monitoring versus Control to Prevent Cognitive Decline in at-Risk Elderly People (FINGER): A Randomised Controlled Trial. *Lancet* **2015**, *385*, 2255–2263. [CrossRef] [PubMed]
96. Palou, A.; Serra, F.; Pico, C. General Aspects on the Assessment of Functional Foods in the European Union. *Eur. J. Clin. Nutr.* **2003**, *57*, S12–S17. [CrossRef] [PubMed]
97. Siró, I.; Kápolna, E.; Kápolna, B.; Lugasi, A. Functional Food. Product Development, Marketing and Consumer Acceptance—A Review. *Appetite* **2008**, *51*, 456–467. [CrossRef]
98. Morkovin, E.; Litvinov, R.; Koushner, A.; Babkov, D. Resveratrol and Extra Virgin Olive Oil: Protective Agents Against Age-Related Disease. *Nutrients* **2024**, *16*, 4258. [CrossRef]
99. Martucci, M.; Conte, M.; Bucci, L.; Giampieri, E.; Fabbri, C.; Palmas, M.G.; Izzi, M.; Salvioli, S.; Zambrini, A.V.; Orsi, C.; et al. Twelve-Week Daily Consumption of Ad Hoc Fortified Milk with ω-3, D, and Group B Vitamins Has a Positive Impact on Inflammaging Parameters: A Randomized Cross-over Trial. *Nutrients* **2020**, *12*, 3580. [CrossRef]
100. Tillisch, K.; Labus, J.; Kilpatrick, L.; Jiang, Z.; Stains, J.; Ebrat, B.; Guyonnet, D.; Legrain–Raspaud, S.; Trotin, B.; Naliboff, B.; et al. Consumption of Fermented Milk Product with Probiotic Modulates Brain Activity. *Gastroenterology* **2013**, *144*, 1394–1401.e4. [CrossRef]
101. Navarro-Hortal, M.D.; Romero-Márquez, J.M.; Jiménez-Trigo, V.; Xiao, J.; Giampieri, F.; Forbes-Hernández, T.Y.; Grosso, G.; Battino, M.; Sánchez-González, C.; Quiles, J.L. Molecular Bases for the Use of Functional Foods in the Management of Healthy Aging: Berries, Curcumin, Virgin Olive Oil and Honey; Three Realities and a Promise. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 11967–11986. [CrossRef]
102. Driver, C. Mitochondrial Interventions in Aging and Longevity. In *Modulating Aging and Longevity*; Springer: Dordrecht, The Netherlands, 2003; pp. 205–217.
103. Reiter, R.J.; Tan, D.X.; Manchester, L.C.; El-Sawi, M.R. Melatonin Reduces Oxidant Damage and Promotes Mitochondrial Respiration: Implications for Aging. *Ann. N. Y. Acad. Sci.* **2002**, *959*, 238–250. [CrossRef]
104. Mahoney, D.J.; Parise, G.; Tarnopolsky, M.A. Nutritional and Exercise-Based Therapies in the Treatment of Mitochondrial Disease. *Curr. Opin. Clin. Nutr. Metab. Care* **2002**, *5*, 619–629. [CrossRef]
105. Ames, B.N.; Shigenaga, M.K.; Hagen, T.M. Oxidants, Antioxidants, and the Degenerative Diseases of Aging. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 7915–7922. [CrossRef]

106. Wissler Gerdes, E.O.; Zhu, Y.; Weigand, B.M.; Tripathi, U.; Burns, T.C.; Tchkonia, T.; Kirkland, J.L. Cellular Senescence in Aging and Age-Related Diseases: Implications for Neurodegenerative Diseases. In *International Review of Neurobiology*; Academic Press Inc.: Cambridge, MA, USA, 2020; Volume 155, pp. 203–234, ISBN 9780128231210.
107. Dhingra, D.; Parle, M.; Kulkarni, S.K. Comparative Brain Cholinesterase-Inhibiting Activity of *Glycyrrhiza Glabra*, *Myristica Fragrans*, Ascorbic Acid, and Metrifonate in Mice. *J. Med. Food* **2006**, *9*, 281–283. [CrossRef] [PubMed]
108. Man Anh, H.; Linh, D.M.; My Dung, V.; Thi Phuong Thao, D. Evaluating Dose- and Time-Dependent Effects of Vitamin C Treatment on a Parkinson's Disease Fly Model. *Park. Dis.* **2019**, *2019*, 9720546. [CrossRef] [PubMed]
109. Casani, S.; Gómez-Pastor, R.; Matallana, E.; Paricio, N. Antioxidant Compound Supplementation Prevents Oxidative Damage in a Drosophila Model of Parkinson's Disease. *Free Radic. Biol. Med.* **2013**, *61*, 151–160. [CrossRef]
110. Huang, J.; May, J.M. Ascorbic Acid Protects SH-SY5Y Neuroblastoma Cells from Apoptosis and Death Induced by β-Amyloid. *Brain Res.* **2006**, *1097*, 52–58. [CrossRef]
111. Rosales-Corral, S.; Tan, D.; Reiter, R.J.; Valdivia-Velázquez, M.; Martínez-Barboza, G.; Pablo Acosta-Martínez, J.; Ortiz, G.G. Orally Administered Melatonin Reduces Oxidative Stress and Proinflammatory Cytokines Induced by Amyloid-β Peptide in Rat Brain: A Comparative, in vivo Study versus Vitamin C and E. *J. Pineal Res.* **2003**, *35*, 80–84. [CrossRef]
112. Jeong, J.H.; Kim, M.B.; Kim, C.; Hwang, J.K. Inhibitory Effect of Vitamin C on Intrinsic Aging in Human Dermal Fibroblasts and Hairless Mice. *Food Sci. Biotechnol.* **2017**, *27*, 555–564. [CrossRef]
113. Teawcharoensopa, C.; Srisuwan, T. The Potential Use of Ascorbic Acid to Recover the Cellular Senescence of Lipopolysaccharide-Induced Human Apical Papilla Cells: An in vitro Study. *Clin. Oral. Investig.* **2023**, *28*, 49. [CrossRef]
114. Schirinzi, T.; Martella, G.; Imbriani, P.; Di Lazzaro, G.; Franco, D.; Colona, V.L.; Alwardat, M.; Sinibaldi Salimei, P.; Mercuri, N.B.; Pierantozzi, M.; et al. Dietary Vitamin E as a Protective Factor for Parkinson's Disease: Clinical and Experimental Evidence. *Front. Neurol.* **2019**, *10*, 148. [CrossRef]
115. Nakaso, K.; Tajima, N.; Horikoshi, Y.; Nakasone, M.; Hanaki, T.; Kamizaki, K.; Matsura, T. The Estrogen Receptor β-PI3K/Akt Pathway Mediates the Cytoprotective Effects of Tocotrienol in a Cellular Parkinson's Disease Model. *Biochim. Biophys. Acta (BBA) Mol. Basis Dis.* **2014**, *1842*, 1303–1312. [CrossRef]
116. Nakaso, K.; Horikoshi, Y.; Takahashi, T.; Hanaki, T.; Nakasone, M.; Kitagawa, Y.; Koike, T.; Matsura, T. Estrogen Receptor-Mediated Effect of δ-Tocotrienol Prevents Neurotoxicity and Motor Deficit in the MPTP Mouse Model of Parkinson's Disease. *Neurosci. Lett.* **2016**, *610*, 117–122. [CrossRef]
117. Perry, T.L.; Yong, V.W.; Clavier, R.M.; Jones, K.; Wright, J.M.; Foulks, J.G.; Wall, R.A. Partial Protection from the Dopaminergic Neurotoxin N-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine by Four Different Antioxidants in the Mouse. *Neurosci. Lett.* **1985**, *60*, 109–114. [CrossRef] [PubMed]
118. Hao, X.; Li, H.; Li, Q.; Gao, D.; Wang, X.; Wu, C.; Wang, Q.; Zhu, M. Dietary Vitamin E Intake and Risk of Parkinson's Disease: A Cross-Sectional Study. *Front. Nutr.* **2024**, *10*, 1289238. [CrossRef] [PubMed]
119. Yatin, S.M.; Varadarajan, S.; Butterfield, D.A. Vitamin E Prevents Alzheimer's Amyloid ß-Peptide (1-42)-Induced Neuronal Protein Oxidation and Reactive Oxygen Species Production. *J. Alzheimer's Dis.* **2000**, *2*, 123–131. [CrossRef]
120. Jiang, Q.; Yin, X.; Lill, M.A.; Danielson, M.L.; Freiser, H.; Huang, J. Long-Chain Carboxychromanols, Metabolites of Vitamin E, Are Potent Inhibitors of Cyclooxygenases. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 20464–20469. [CrossRef]
121. Jiang, Q.; Elson-Schwab, I.; Courtemanche, C.; Ames, B.N. γ-Tocopherol and Its Major Metabolite, in Contrast to α-Tocopherol, Inhibit Cyclooxygenase Activity in Macrophages and Epithelial Cells. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 11494–11499. [CrossRef]
122. La Fata, G.; Seifert, N.; Weber, P.; Mohajeri, M.H. Vitamin E Supplementation Delays Cellular Senescence In vitro. *Biomed. Res. Int.* **2015**, *2015*, 563247. [CrossRef]
123. Ricciarelli, R.; Azzi, A.; Zingg, J. Reduction of Senescence-associated Beta-galactosidase Activity by Vitamin E in Human Fibroblasts Depends on Subjects' Age and Cell Passage Number. *BioFactors* **2020**, *46*, 665–674. [CrossRef]
124. Takasaki, J.; Ono, K.; Yoshiike, Y.; Hirohata, M.; Ikeda, T.; Morinaga, A.; Takashima, A.; Yamada, M. Vitamin A Has Anti-Oligomerization Effects on Amyloid-β in vitro. *J. Alzheimer's Dis.* **2011**, *27*, 271–280. [CrossRef]
125. Jarvis, C.I.; Goncalves, M.B.; Clarke, E.; Dogruel, M.; Kalindjian, S.B.; Thomas, S.A.; Maden, M.; Corcoran, J.P.T. Retinoic Acid Receptor-α Signalling Antagonizes Both Intracellular and Extracellular Amyloid-β Production and Prevents Neuronal Cell Death Caused by Amyloid-β. *Eur. J. Neurosci.* **2010**, *32*, 1246–1255. [CrossRef]
126. Kunzler, A.; Zeidán-Chuliá, F.; Gasparotto, J.; Girardi, C.S.; Klafke, K.; Petiz, L.L.; Bortolin, R.C.; Rostirolla, D.C.; Zanotto-Filho, A.; de Bittencourt Pasquali, M.A.; et al. Changes in Cell Cycle and Up-Regulation of Neuronal Markers During SH-SY5Y Neurodifferentiation by Retinoic Acid Are Mediated by Reactive Species Production and Oxidative Stress. *Mol. Neurobiol.* **2017**, *54*, 6903–6916. [CrossRef]
127. Pan, J.; Yu, J.; Sun, L.; Xie, C.; Chang, L.; Wu, J.; Hawes, S.; Saez–Atienzar, S.; Zheng, W.; Kung, J.; et al. ALDH1A1 Regulates Postsynaptic μ–Opioid Receptor Expression in Dorsal Striatal Projection Neurons and Mitigates Dyskinesia through Transsynaptic Retinoic Acid Signaling. *Sci. Rep.* **2019**, *9*, 3602. [CrossRef] [PubMed]

128. Chen, H.; Liu, S.; Ji, L.; Wu, T.; Ji, Y.; Zhou, Y.; Zheng, M.; Zhang, M.; Xu, W.; Huang, G. Folic Acid Supplementation Mitigates Alzheimer's Disease by Reducing Inflammation: A Randomized Controlled Trial. *Mediat. Inflamm.* **2016**, *2016*, 5912146. [CrossRef] [PubMed]
129. Lee, C.Y.; Chan, L.; Hu, C.J.; Hong, C.T.; Chen, J.H. Role of Vitamin B12 and Folic Acid in Treatment of Alzheimer's Disease: A Meta-Analysis of Randomized Control Trials. *Aging* **2024**, *16*, 7856–7869. [CrossRef]
130. Li, Z.; Zhou, D.; Zhang, D.; Zhao, J.; Li, W.; Sun, Y.; Chen, Y.; Liu, H.; Wilson, J.X.; Qian, Z.; et al. Folic Acid Inhibits Aging-Induced Telomere Attrition and Apoptosis in Astrocytes in vivo and in vitro. *Cereb. Cortex* **2022**, *32*, 286–297. [CrossRef]
131. Rzepka, Z.; Rok, J.; Kowalska, J.; Banach, K.; Wrześniok, D. Cobalamin Deficiency May Induce Astrosenescence—An In vitro Study. *Cells* **2022**, *11*, 3408. [CrossRef]
132. Bientinesi, E.; Lulli, M.; Becatti, M.; Ristori, S.; Margheri, F.; Monti, D. Doxorubicin-Induced Senescence in Normal Fibroblasts Promotes in vitro Tumour Cell Growth and Invasiveness: The Role of Quercetin in Modulating These Processes. *Mech. Ageing Dev.* **2022**, *206*, 111689. [CrossRef]
133. Bientinesi, E.; Ristori, S.; Lulli, M.; Monti, D. Quercetin Induces Senolysis of Doxorubicin-Induced Senescent Fibroblasts by Reducing Autophagy, Preventing Their pro-Tumour Effect on Osteosarcoma Cells. *Mech. Ageing Dev.* **2024**, *220*, 111957. [CrossRef]
134. Maurya, P.K.; Kumar, P.; Nagotu, S.; Chand, S.; Chandra, P. Multi-Target Detection of Oxidative Stress Biomarkers in Quercetin and Myricetin Treated Human Red Blood Cells. *RSC Adv.* **2016**, *6*, 53195–53202. [CrossRef]
135. Zhang, P.; Kishimoto, Y.; Grammatikakis, I.; Gottimukkala, K.; Cutler, R.G.; Zhang, S.; Abdelmohsen, K.; Bohr, V.A.; Misra Sen, J.; Gorospe, M.; et al. Senolytic Therapy Alleviates Aβ-Associated Oligodendrocyte Progenitor Cell Senescence and Cognitive Deficits in an Alzheimer's Disease Model. *Nat. Neurosci.* **2019**, *22*, 719–728. [CrossRef]
136. Rojas, P.; Serrano-García, N.; Mares-Sámano, J.J.; Medina-Campos, O.N.; Pedraza-Chaverri, J.; Ögren, S.O. EGb761 Protects against Nigrostriatal Dopaminergic Neurotoxicity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism in Mice: Role of Oxidative Stress. *Eur. J. Neurosci.* **2008**, *28*, 41–50. [CrossRef]
137. Wu, W.R.; Zhu, X.Z. Involvement of Monoamine Oxidase Inhibition in Neuroprotective and Neurorestorative Effects of Ginkgo Biloba Extract against MPTP-Induced Nigrostriatal Dopaminergic Toxicity in C57 Mice. *Life Sci.* **1999**, *65*, 157–164. [CrossRef] [PubMed]
138. Guo, S.; Yan, J.; Yang, T.; Yang, X.; Bezard, E.; Zhao, B. Protective Effects of Green Tea Polyphenols in the 6-OHDA Rat Model of Parkinson's Disease Through Inhibition of ROS-NO Pathway. *Biol. Psychiatry* **2007**, *62*, 1353–1362. [CrossRef] [PubMed]
139. Albani, D.; Polito, L.; Batelli, S.; De Mauro, S.; Fracasso, C.; Martelli, G.; Colombo, L.; Manzoni, C.; Salmona, M.; Caccia, S.; et al. The SIRT1 Activator Resveratrol Protects SK-N-BE Cells from Oxidative Stress and against Toxicity Caused by α-Synuclein or Amyloid-β (1-42) Peptide. *J. Neurochem.* **2009**, *110*, 1445–1456. [CrossRef]
140. Palazzi, L.; Bruzzone, E.; Bisello, G.; Leri, M.; Stefani, M.; Bucciantini, M.; Polverino de Laureto, P. Oleuropein Aglycone Stabilizes the Monomeric α-Synuclein and Favours the Growth of Non-Toxic Aggregates. *Sci. Rep.* **2018**, *8*, 8337. [CrossRef]
141. Mohammad-Beigi, H.; Aliakbari, F.; Sahin, C.; Lomax, C.; Tawfike, A.; Schafer, N.P.; Amiri-Nowdijeh, A.; Eskandari, H.; Møller, I.M.; Hosseini-Mazinani, M.; et al. Oleuropein Derivatives from Olive Fruit Extracts Reduce α-Synuclein Fibrillation and Oligomer Toxicity. *J. Biol. Chem.* **2019**, *294*, 4215–4232. [CrossRef]
142. Currais, A.; Farrokhi, C.; Dargusch, R.; Armando, A.; Quehenberger, O.; Schubert, D.; Maher, P. Fisetin Reduces the Impact of Aging on Behavior and Physiology in the Rapidly Aging SAMP8 Mouse. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2018**, *73*, 299–307. [CrossRef]
143. Papanastasiou, S.A.; Bali, E.-M.D.; Ioannou, C.S.; Papachristos, D.P.; Zarpas, K.D.; Papadopoulos, N.T. Toxic and Hormetic-like Effects of Three Components of Citrus Essential Oils on Adult Mediterranean Fruit Flies (Ceratitis Capitata). *PLoS ONE* **2017**, *12*, e0177837. [CrossRef]
144. Hou, J.; Cui, C.; Kim, S.; Sung, C.; Choi, C. Ginsenoside F1 Suppresses Astrocytic Senescence-Associated Secretory Phenotype. *Chem. Biol. Interact.* **2018**, *283*, 75–83. [CrossRef]
145. Cao, G.; Su, P.; Zhang, S.; Guo, L.; Zhang, H.; Liang, Y.; Qin, C.; Zhang, W. Ginsenoside Re Reduces Aβ Production by Activating PPARγ to Inhibit BACE1 in N2a/APP695 Cells. *Eur. J. Pharmacol.* **2016**, *793*, 101–108. [CrossRef]
146. Chougouo, R.D.K.; Nguekeu, Y.M.M.; Dzoyem, J.P.; Awouafack, M.D.; Kouamouo, J.; Tane, P.; McGaw, L.J.; Eloff, J.N. Anti-Inflammatory and Acetylcholinesterase Activity of Extract, Fractions and Five Compounds Isolated from the Leaves and Twigs of Artemisia Annua Growing in Cameroon. *SpringerPlus* **2016**, *5*, 1525. [CrossRef]
147. Xia, M.L.; Xie, X.H.; Ding, J.H.; Du, R.H.; Hu, G. Astragaloside IV Inhibits Astrocyte Senescence: Implication in Parkinson's Disease. *J. Neuroinflamm.* **2020**, *17*, 105. [CrossRef] [PubMed]
148. Scapagnini, G.; Colombrita, C.; Amadio, M.; D'Agata, V.; Arcelli, E.; Sapienza, M.; Quattrone, A.; Calabrese, V. Curcumin Activates Defensive Genes and Protects Neurons Against Oxidative Stress. *Antioxid. Redox Signal.* **2006**, *8*, 395–403. [CrossRef] [PubMed]

149. Yang, F.; Lim, G.P.; Begum, A.N.; Ubeda, O.J.; Simmons, M.R.; Ambegaokar, S.S.; Chen, P.; Kayed, R.; Glabe, C.G.; Frautschy, S.A.; et al. Curcumin Inhibits Formation of Amyloid β Oligomers and Fibrils, Binds Plaques, and Reduces Amyloid in vivo. *J. Biol. Chem.* **2005**, *280*, 5892–5901. [CrossRef] [PubMed]
150. Taka, T.; Changtam, C.; Thaichana, P.; Kaewtunjai, N.; Suksamrarn, A.; Lee, T.R.; Tuntiwechapikul, W. Curcuminoid Derivatives Enhance Telomerase Activity in an in vitro TRAP Assay. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5242–5246. [CrossRef]
151. Zbarsky, V.; Datla, K.P.; Parkar, S.; Rai, D.K.; Aruoma, O.I.; Dexter, D.T. Neuroprotective Properties of the Natural Phenolic Antioxidants Curcumin and Naringenin but Not Quercetin and Fisetin in a 6-OHDA Model of Parkinson's Disease. *Free Radic. Res.* **2005**, *39*, 1119–1125. [CrossRef]
152. Wang, J.; Du, X.-X.; Jiang, H.; Xie, J.-X. Curcumin Attenuates 6-Hydroxydopamine-Induced Cytotoxicity by Anti-Oxidation and Nuclear Factor-KappaB Modulation in MES23.5 Cells. *Biochem. Pharmacol.* **2009**, *78*, 178–183. [CrossRef]
153. Zhang, L.; Fiala, M.; Cashman, J.; Sayre, J.; Espinosa, A.; Mahanian, M.; Zaghi, J.; Badmaev, V.; Graves, M.C.; Bernard, G.; et al. Curcuminoids Enhance Amyloid-β Uptake by Macrophages of Alzheimer's Disease Patients. *J. Alzheimer's Dis.* **2006**, *10*, 1–7. [CrossRef]
154. Kim, D.S.H.L.; Park, S.Y.; Kim, J.Y. Curcuminoids from Curcuma Longa L. (Zingiberaceae) That Protect PC12 Rat Pheochromocytoma and Normal Human Umbilical Vein Endothelial Cells from BA(1–42) Insult. *Neurosci. Lett.* **2001**, *303*, 57–61. [CrossRef]
155. Liu, H.; Li, Z.; Qiu, D.; Gu, Q.; Lei, Q.; Mao, L. The Inhibitory Effects of Different Curcuminoids on β-Amyloid Protein, β-Amyloid Precursor Protein and β-Site Amyloid Precursor Protein Cleaving Enzyme 1 in SwAPP HEK293 Cells. *Neurosci. Lett.* **2010**, *485*, 83–88. [CrossRef]
156. Ono, K.; Hasegawa, K.; Naiki, H.; Yamada, M. Curcumin Has Potent Anti-amyloidogenic Effects for Alzheimer's B-amyloid Fibrils in vitro. *J. Neurosci. Res.* **2004**, *75*, 742–750. [CrossRef]
157. Yang, W.; Chen, Y.H.; Liu, H.; Qu, H.D. Neuroprotective Effects of Piperine on the 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Induced Parkinson's Disease Mouse Model. *Int. J. Mol. Med.* **2015**, *36*, 1369–1376. [CrossRef] [PubMed]
158. Chonpathompikunlert, P.; Wattanathorn, J.; Muchimapura, S. Piperine, the Main Alkaloid of Thai Black Pepper, Protects against Neurodegeneration and Cognitive Impairment in Animal Model of Cognitive Deficit like Condition of Alzheimer's Disease. *Food Chem. Toxicol.* **2010**, *48*, 798–802. [CrossRef] [PubMed]
159. Subedee, L. Preventive Role of Indian Black Pepper in Animal Models of Alzheimer's Disease. *J. Clin. Diagn. Res.* **2015**, *9*, FF01–FF04. [CrossRef]
160. Bae, W.-Y.; Choi, J.-S.; Jeong, J.-W. The Neuroprotective Effects of Cinnamic Aldehyde in an MPTP Mouse Model of Parkinson's Disease. *Int. J. Mol. Sci.* **2018**, *19*, 551. [CrossRef]
161. Ramazani, E.; YazdFazeli, M.; Emami, S.A.; Mohtashami, L.; Javadi, B.; Asili, J.; Tayarani-Najaran, Z. Protective Effects of Cinnamomum Verum, Cinnamomum Cassia and Cinnamaldehyde against 6-OHDA-Induced Apoptosis in PC12 Cells. *Mol. Biol. Rep.* **2020**, *47*, 2437–2445. [CrossRef]
162. Shaltiel-Karyo, R.; Davidi, D.; Frenkel-Pinter, M.; Ovadia, M.; Segal, D.; Gazit, E. Differential Inhibition of α-Synuclein Oligomeric and Fibrillar Assembly in Parkinson's Disease Model by Cinnamon Extract. *Biochim. Biophys. Acta (BBA) Gen. Subj.* **2012**, *1820*, 1628–1635. [CrossRef]
163. Schink, A.; Naumoska, K.; Kitanovski, Z.; Kampf, C.J.; Fröhlich-Nowoisky, J.; Thines, E.; Pöschl, U.; Schuppan, D.; Lucas, K. Anti-Inflammatory Effects of Cinnamon Extract and Identification of Active Compounds Influencing the TLR2 and TLR4 Signaling Pathways. *Food Funct.* **2018**, *9*, 5950–5964. [CrossRef]
164. Frydman-Marom, A.; Levin, A.; Farfara, D.; Benromano, T.; Scherzer-Attali, R.; Peled, S.; Vassar, R.; Segal, D.; Gazit, E.; Frenkel, D.; et al. Orally Administrated Cinnamon Extract Reduces β-Amyloid Oligomerization and Corrects Cognitive Impairment in Alzheimer's Disease Animal Models. *PLoS ONE* **2011**, *6*, e16564. [CrossRef]
165. Auti, S.T.; Kulkarni, Y.A. Neuroprotective Effect of Cardamom Oil Against Aluminum Induced Neurotoxicity in Rats. *Front. Neurol.* **2019**, *10*, 399. [CrossRef]
166. Matt, S.M.; Allen, J.M.; Lawson, M.A.; Mailing, L.J.; Woods, J.A.; Johnson, R.W. Butyrate and Dietary Soluble Fiber Improve Neuroinflammation Associated with Aging in Mice. *Front. Immunol.* **2018**, *9*, 386847. [CrossRef]
167. Ho, L.; Ono, K.; Tsuji, M.; Mazzola, P.; Singh, R.; Pasinetti, G.M. Protective Roles of Intestinal Microbiota Derived Short Chain Fatty Acids in Alzheimer's Disease-Type Beta-Amyloid Neuropathological Mechanisms. *Expert. Rev. Neurother.* **2018**, *18*, 83–90. [CrossRef] [PubMed]
168. Zhou, Y.; Xie, L.; Schröder, J.; Schuster, I.S.; Nakai, M.; Sun, G.; Sun, Y.B.Y.; Mariño, E.; Degli-Esposti, M.A.; Marques, F.Z.; et al. Dietary Fiber and Microbiota Metabolite Receptors Enhance Cognition and Alleviate Disease in the 5xFAD Mouse Model of Alzheimer's Disease. *J. Neurosci.* **2023**, *43*, 6460–6475. [CrossRef] [PubMed]
169. Woo, J.Y.; Gu, W.; Kim, K.A.; Jang, S.E.; Han, M.J.; Kim, D.H. Lactobacillus Pentosus Var. Plantarum C29 Ameliorates Memory Impairment and Inflammaging in a d-Galactose-Induced Accelerated Aging Mouse Model. *Anaerobe* **2014**, *27*, 22–26. [CrossRef]

170. Grompone, G.; Martorell, P.; Llopis, S.; González, N.; Genovés, S.; Mulet, A.P.; Fernández-Calero, T.; Tiscornia, I.; Bollati-Fogolín, M.; Chambaud, I.; et al. Anti-Inflammatory Lactobacillus Rhamnosus CNCM I-3690 Strain Protects against Oxidative Stress and Increases Lifespan in Caenorhabditis Elegans. *PLoS ONE* **2012**, *7*, e52493. [CrossRef]
171. Lin, X.; Xia, Y.; Wang, G.; Xiong, Z.; Zhang, H.; Lai, F.; Ai, L. Lactobacillus Plantarum AR501 Alleviates the Oxidative Stress of D-Galactose-Induced Aging Mice Liver by Upregulation of Nrf2-Mediated Antioxidant Enzyme Expression. *J. Food Sci.* **2018**, *83*, 1990–1998. [CrossRef]
172. Magistrelli, L.; Amoruso, A.; Mogna, L.; Graziano, T.; Cantello, R.; Pane, M.; Comi, C. Probiotics May Have Beneficial Effects in Parkinson's Disease: In vitro Evidence. *Front. Immunol.* **2019**, *10*, 969. [CrossRef]
173. Castelli, V.; D'Angelo, M.; Lombardi, F.; Alfonsetti, M.; Antonosante, A.; Catanesi, M.; Benedetti, E.; Palumbo, P.; Cifone, M.G.; Giordano, A.; et al. Effects of the Probiotic Formulation SLAB51 in in vitro and in vivo Parkinson's Disease Models. *Aging* **2020**, *12*, 4641–4659. [CrossRef]
174. Liao, J.F.; Cheng, Y.F.; You, S.T.; Kuo, W.C.; Huang, C.W.; Chiou, J.J.; Hsu, C.C.; Hsieh-Li, H.M.; Wang, S.; Tsai, Y.C. Lactobacillus Plantarum PS128 Alleviates Neurodegenerative Progression in 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Induced Mouse Models of Parkinson's Disease. *Brain Behav. Immun.* **2020**, *90*, 26–46. [CrossRef]
175. Srivastav, S.; Neupane, S.; Bhurtel, S.; Katila, N.; Maharjan, S.; Choi, H.; Hong, J.T.; Choi, D.Y. Probiotics Mixture Increases Butyrate, and Subsequently Rescues the Nigral Dopaminergic Neurons from MPTP and Rotenone-Induced Neurotoxicity. *J. Nutr. Biochem.* **2019**, *69*, 73–86. [CrossRef]
176. Jeong, J.J.; Woo, J.Y.; Kim, K.A.; Han, M.J.; Kim, D.H. Lactobacillus Pentosus Var. Plantarum C29 Ameliorates Age-Dependent Memory Impairment in Fischer 344 Rats. *Lett. Appl. Microbiol.* **2015**, *60*, 307–314. [CrossRef]
177. Kobayashi, Y.; Sugahara, H.; Shimada, K.; Mitsuyama, E.; Kuhara, T.; Yasuoka, A.; Kondo, T.; Abe, K.; Xiao, J.Z. Therapeutic Potential of Bifidobacterium Breve Strain A1 for Preventing Cognitive Impairment in Alzheimer's Disease. *Sci. Rep.* **2017**, *7*, 13510. [CrossRef] [PubMed]
178. Hall, D.A.; Voigt, R.M.; Cantu-Jungles, T.M.; Hamaker, B.; Engen, P.A.; Shaikh, M.; Raeisi, S.; Green, S.J.; Naqib, A.; Forsyth, C.B.; et al. An Open Label, Non-Randomized Study Assessing a Prebiotic Fiber Intervention in a Small Cohort of Parkinson's Disease Participants. *Nat. Commun.* **2023**, *14*, 926. [CrossRef] [PubMed]
179. Becker, A.; Schmartz, G.P.; Gröger, L.; Grammes, N.; Galata, V.; Philippeit, H.; Weiland, J.; Ludwig, N.; Meese, E.; Tierling, S.; et al. Effects of Resistant Starch on Symptoms, Fecal Markers, and Gut Microbiota in Parkinson's Disease—The RESISTA-PD Trial. *Genom. Proteom. Bioinform.* **2022**, *20*, 274–287. [CrossRef]
180. Chen, D.; Yang, X.; Yang, J.; Lai, G.; Yong, T.; Tang, X.; Shuai, O.; Zhou, G.; Xie, Y.; Wu, Q. Prebiotic Effect of Fructooligosaccharides from Morinda Officinalis on Alzheimer's Disease in Rodent Models by Targeting the Microbiota-Gut-Brain Axis. *Front. Aging Neurosci.* **2017**, *9*, 403. [CrossRef]
181. Bousquet, M.; Saint-Pierre, M.; Julien, C.; Salem, N.; Cicchetti, F.; Calon, F. Beneficial Effects of Dietary Omega-3 Polyunsaturated Fatty Acid on Toxin-induced Neuronal Degeneration in an Animal Model of Parkinson's Disease. *FASEB J.* **2008**, *22*, 1213–1225. [CrossRef] [PubMed]
182. De Lau, L.M.L.; Bornebroek, M.; Witteman, J.C.M.; Hofman, A.; Koudstaal, P.J.; Breteler, M.M.B. Dietary Fatty Acids and the Risk of Parkinson Disease: The Rotterdam Study. *Neurology* **2005**, *64*, 2040–2045. [CrossRef]
183. Kamel, F.; Goldman, S.M.; Umbach, D.M.; Chen, H.; Richardson, G.; Barber, M.R.; Meng, C.; Marras, C.; Korell, M.; Kasten, M.; et al. Dietary Fat Intake, Pesticide Use, and Parkinson's Disease. *Park. Relat. Disord.* **2014**, *20*, 82–87. [CrossRef]
184. Bousquet, M.; Gibrat, C.; Saint-Pierre, M.; Julien, C.; Calon, F.; Cicchetti, F. Modulation of Brain-Derived Neurotrophic Factor as a Potential Neuroprotective Mechanism of Action of Omega-3 Fatty Acids in a Parkinsonian Animal Model. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2009**, *33*, 1401–1408. [CrossRef] [PubMed]
185. Morgese, M.G.; Schiavone, S.; Bove, M.; Colia, A.L.; Dimonte, S.; Tucci, P.; Trabace, L. N-3 PUFA Prevent Oxidative Stress in a Rat Model of Beta-Amyloid-Induced Toxicity. *Pharmaceuticals* **2021**, *14*, 339. [CrossRef]
186. Faxén-Irving, G.; Freund-Levi, Y.; Eriksdotter-Jönhagen, M.; Basun, H.; Hjorth, E.; Palmblad, J.; Vedin, I.; Cederholm, T.; Wahlund, L.O. Effects on Transthyretin in Plasma and Cerebrospinal Fluid by Dha-Rich n-3 Fatty Acid Supplementation in Patients with Alzheimer's Disease: The Omegad Study. *J. Alzheimer's Dis.* **2013**, *36*, 1–6. [CrossRef]
187. Calon, F.; Lim, G.P.; Yang, F.; Morihara, T.; Teter, B.; Ubeda, O.; Rostaing, P.; Triller, A.; Salem, N.; Ashe, K.H.; et al. Docosahexaenoic Acid Protects from Dendritic Pathology in an Alzheimer's Disease Mouse Model. *Neuron* **2004**, *43*, 633–645. [CrossRef] [PubMed]
188. Arsenault, D.; Julien, C.; Tremblay, C.; Calon, F. DHA Improves Cognition and Prevents Dysfunction of Entorhinal Cortex Neurons in 3xTg-AD Mice. *PLoS ONE* **2011**, *6*, e17397. [CrossRef] [PubMed]
189. Casali, B.T.; Corona, A.W.; Mariani, M.M.; Karlo, J.C.; Ghosal, K.; Landreth, G.E. Omega-3 Fatty Acids Augment the Actions of Nuclear Receptor Agonists in a Mouse Model of Alzheimer's Disease. *J. Neurosci.* **2015**, *35*, 9173–9181. [CrossRef]

190. Perez, S.E.; Berg, B.M.; Moore, K.A.; He, B.; Counts, S.E.; Fritz, J.J.; Hu, Y.S.; Lazarov, O.; Lah, J.J.; Mufson, E.J. DHA Diet Reduces AD Pathology in Young APPswe/PS1ΔE9 Transgenic Mice: Possible Gender Effects. *J. Neurosci. Res.* **2010**, *88*, 1026–1040. [CrossRef]
191. Lyras, L.; Cairns, N.J.; Jenner, A.; Jenner, P.; Halliwell, B. An Assessment of Oxidative Damage to Proteins, Lipids, and DNA in Brain from Patients with Alzheimer's Disease. *J. Neurochem.* **1997**, *68*, 2061–2069. [CrossRef]
192. Bej, E.; Cesare, P.; Volpe, A.R.; d'Angelo, M.; Castelli, V. Oxidative Stress and Neurodegeneration: Insights and Therapeutic Strategies for Parkinson's Disease. *Neurol. Int.* **2024**, *16*, 502–517. [CrossRef]
193. May, J.M. Vitamin C Transport and Its Role in the Central Nervous System. In *Water Soluble Vitamins*; Springer: Dordrecht, The Netherlands, 2012; pp. 85–103.
194. Harrison, F.E.; May, J.M. Vitamin C Function in the Brain: Vital Role of the Ascorbate Transporter SVCT2. *Free Radic. Biol. Med.* **2009**, *46*, 719–730. [CrossRef]
195. Harrison, F.E.; Hosseini, A.H.; McDonald, M.P.; May, J.M. Vitamin C Reduces Spatial Learning Deficits in Middle-Aged and Very Old APP/PSEN1 Transgenic and Wild-Type Mice. *Pharmacol. Biochem. Behav.* **2009**, *93*, 443–450. [CrossRef]
196. Lee, J.; Chang, M.; Park, C.; Kim, H.; Kim, J.; Son, H.; Lee, Y.; Lee, S. Ascorbate-induced Differentiation of Embryonic Cortical Precursors into Neurons and Astrocytes. *J. Neurosci. Res.* **2003**, *73*, 156–165. [CrossRef]
197. Harrison, F.; Bowman, G.; Polidori, M. Ascorbic Acid and the Brain: Rationale for the Use against Cognitive Decline. *Nutrients* **2014**, *6*, 1752–1781. [CrossRef]
198. Nualart, F. Vitamin C Transporters, Recycling and the Bystander Effect in the Nervous System: SVCT2 versus Gluts. *J. Stem Cell Res. Ther.* **2014**, *4*, 1–11. [CrossRef] [PubMed]
199. Belluzzi, E.; Bisaglia, M.; Lazzarini, E.; Tabares, L.C.; Beltramini, M.; Bubacco, L. Human SOD2 Modification by Dopamine Quinones Affects Enzymatic Activity by Promoting Its Aggregation: Possible Implications for Parkinson's Disease. *PLoS ONE* **2012**, *7*, e38026. [CrossRef] [PubMed]
200. Etminan, M.; Gill, S.S.; Samii, A. Intake of Vitamin E, Vitamin C, and Carotenoids and the Risk of Parkinson's Disease: A Meta-Analysis. *Lancet Neurol.* **2005**, *4*, 362–365. [CrossRef]
201. Grünewald, R.A. Ascorbic Acid in the Brain. *Brain Res. Rev.* **1993**, *18*, 123–133. [CrossRef]
202. Mefford, I.N.; Oke, A.F.; Adams, R.N. Regional Distribution of Ascorbate in Human Brain. *Brain Res.* **1981**, *212*, 223–226. [CrossRef]
203. Figueroa-Méndez, R.; Rivas-Arancibia, S. Vitamin C in Health and Disease: Its Role in the Metabolism of Cells and Redox State in the Brain. *Front. Physiol.* **2015**, *6*, 397. [CrossRef]
204. Seitz, G.; Gebhardt, S.; Beck, J.F.; Böhm, W.; Lode, H.N.; Niethammer, D.; Bruchelt, G. Ascorbic Acid Stimulates DOPA Synthesis and Tyrosine Hydroxylase Gene Expression in the Human Neuroblastoma Cell Line SK-N-SH. *Neurosci. Lett.* **1998**, *244*, 33–36. [CrossRef]
205. Nagayama, H.; Hamamoto, M.; Ueda, M.; Nito, C.; Yamaguchi, H.; Katayama, Y. The Effect of Ascorbic Acid on the Pharmacokinetics of Levodopa in Elderly Patients with Parkinson Disease. *Clin. Neuropharmacol.* **2004**, *27*, 270–273. [CrossRef]
206. Nikolova, G.; Karamalakova, Y.; Gadjeva, V. Reducing Oxidative Toxicity of L-Dopa in Combination with Two Different Antioxidants: An Essential Oil Isolated from Rosa Damascena Mill., and Vitamin C. *Toxicol. Rep.* **2019**, *6*, 267–271. [CrossRef]
207. Yan, J.; Studer, L.; McKay, R.D.G. Ascorbic Acid Increases the Yield of Dopaminergic Neurons Derived from Basic Fibroblast Growth Factor Expanded Mesencephalic Precursors. *J. Neurochem.* **2001**, *76*, 307–311. [CrossRef]
208. Hughes, K.C.; Gao, X.; Kim, I.Y.; Rimm, E.B.; Wang, M.; Weisskopf, M.G.; Schwarzschild, M.A.; Ascherio, A. Intake of Antioxidant Vitamins and Risk of Parkinson's Disease. *Mov. Disord.* **2016**, *31*, 1909–1914. [CrossRef] [PubMed]
209. Yang, F.; Wolk, A.; Håkansson, N.; Pedersen, N.L.; Wirdefeldt, K. Dietary Antioxidants and Risk of Parkinson's Disease in Two Population-based Cohorts. *Mov. Disord.* **2017**, *32*, 1631–1636. [CrossRef] [PubMed]
210. Miyake, Y.; Fukushima, W.; Tanaka, K.; Sasaki, S.; Kiyohara, C.; Tsuboi, Y.; Yamada, T.; Oeda, T.; Miki, T.; Kawamura, N.; et al. Dietary Intake of Antioxidant Vitamins and Risk of Parkinson's Disease: A Case–Control Study in Japan. *Eur. J. Neurol.* **2011**, *18*, 106–113. [CrossRef]
211. Cohen, G.; Kesler, N. Monoamine Oxidase and Mitochondrial Respiration. *J. Neurochem.* **1999**, *73*, 2310–2315. [CrossRef]
212. Odunze, I.N.; Klaidman, L.K.; Adams, J.D. MPTP Toxicity in the Mouse Brain and Vitamin E. *Neurosci. Lett.* **1990**, *108*, 346–349. [CrossRef]
213. Feng, Y.; Wang, X. Antioxidant Therapies for Alzheimer's Disease. *Oxid. Med. Cell Longev.* **2012**, *2012*, 472932. [CrossRef]
214. Monacelli, F.; Acquarone, E.; Giannotti, C.; Borghi, R.; Nencioni, A. Vitamin C, Aging and Alzheimer's Disease. *Nutrients* **2017**, *9*, 670. [CrossRef]
215. Niki, E. Role of Vitamin E as a Lipid-Soluble Peroxyl Radical Scavenger: In vitro and in vivo Evidence. *Free Radic. Biol. Med.* **2014**, *66*, 3–12. [CrossRef]
216. Ulatowski, L.M.; Manor, D. Vitamin E and Neurodegeneration. *Neurobiol. Dis.* **2015**, *84*, 78–83. [CrossRef]

217. Scimemi, A.; Meabon, J.S.; Woltjer, R.L.; Sullivan, J.M.; Diamond, J.S.; Cook, D.G. Amyloid-β $_{1–42}$ Slows Clearance of Synaptically Released Glutamate by Mislocalizing Astrocytic GLT-1. *J. Neurosci.* **2013**, *33*, 5312–5318. [CrossRef]
218. Mattson, M.P. Pathways towards and Away from Alzheimer's Disease. *Nature* **2004**, *430*, 631–639. [CrossRef] [PubMed]
219. Lee, H.P.; Casadesus, G.; Zhu, X.; Lee, H.G.; Perry, G.; Smith, M.A.; Gustaw-Rothenberg, K.; Lerner, A. All-Trans Retinoic Acid as a Novel Therapeutic Strategy for Alzheimer's Disease. *Expert. Rev. Neurother.* **2009**, *9*, 1615–1621. [CrossRef] [PubMed]
220. Blaner, W.S.; Shmarakov, I.O.; Traber, M.G. Vitamin A and Vitamin E: Will the Real Antioxidant Please Stand Up? *Annu. Rev. Nutr.* **2025**, *59*, 17. [CrossRef] [PubMed]
221. Marie, A.; Darricau, M.; Touyarot, K.; Parr-Brownlie, L.C.; Bosch-Bouju, C. Role and Mechanism of Vitamin A Metabolism in the Pathophysiology of Parkinson's Disease. *J. Park. Dis.* **2021**, *11*, 949–970. [CrossRef]
222. McCaffery, P.; Zhang, J.; Crandall, J.E. Retinoic Acid Signaling and Function in the Adult Hippocampus. *J. Neurobiol.* **2006**, *66*, 780–791. [CrossRef]
223. Lyon, P.; Strippoli, V.; Fang, B.; Cimmino, L. B Vitamins and One-Carbon Metabolism: Implications in Human Health and Disease. *Nutrients* **2020**, *12*, 2867. [CrossRef]
224. Pusceddu, I.; Herrmann, W.; Kleber, M.E.; Scharnagl, H.; März, W.; Herrmann, M. Telomere Length, Vitamin B12 and Mortality in Persons Undergoing Coronary Angiography: The Ludwigshafen Risk and Cardiovascular Health Study. *Aging* **2019**, *11*, 7083–7097. [CrossRef]
225. Praveen, G.; Sivaprasad, M.; Reddy, G.B. Telomere Length and Vitamin B12. In *Vitamins and Hormones*; Academic Press Inc.: Cambridge, MA, USA, 2022; Volume 119, pp. 299–324, ISBN 9780323992237.
226. Xin, H.; Liu, D.; Songyang, Z. The Telosome/Shelterin Complex and Its Functions. *Genome Biol.* **2008**, *9*, 232. [CrossRef]
227. Mandel, S.A.; Amit, T.; Weinreb, O.; Youdim, M.B.H. Understanding the Broad-Spectrum Neuroprotective Action Profile of Green Tea Polyphenols in Aging and Neurodegenerative Diseases. *J. Alzheimer's Dis.* **2011**, *25*, 187–208. [CrossRef]
228. Williams, R.J.; Spencer, J.P.E.; Rice-Evans, C. Flavonoids: Antioxidants or Signalling Molecules? *Free Radic. Biol. Med.* **2004**, *36*, 838–849. [CrossRef]
229. Menicacci, B.; Cipriani, C.; Margheri, F.; Mocali, A.; Giovannelli, L. Modulation of the Senescence-Associated Inflammatory Phenotype in Human Fibroblasts by Olive Phenols. *Int. J. Mol. Sci.* **2017**, *18*, 2275. [CrossRef] [PubMed]
230. Lim, H.; Park, H.; Kim, H.P. Effects of Flavonoids on Senescence-Associated Secretory Phenotype Formation from Bleomycin-Induced Senescence in BJ Fibroblasts. *Biochem. Pharmacol.* **2015**, *96*, 337–348. [CrossRef] [PubMed]
231. Sadruddin, S.; Arora, R. Resveratrol: Biologic and Therapeutic Implications. *J. Cardiometab. Syndr.* **2009**, *4*, 102–106. [CrossRef]
232. Jung, U.J.; Kim, S.R. Beneficial Effects of Flavonoids Against Parkinson's Disease. *J. Med. Food* **2018**, *21*, 421–432. [CrossRef]
233. Levites, Y.; Youdim, M.B.H.; Maor, G.; Mandel, S. Attenuation of 6-Hydroxydopamine (6-OHDA)-Induced Nuclear Factor-KappaB (NF-KB) Activation and Cell Death by Tea Extracts in Neuronal Cultures. *Biochem. Pharmacol.* **2002**, *63*, 21–29. [CrossRef]
234. Khan, M.M.; Ahmad, A.; Ishrat, T.; Khan, M.B.; Hoda, M.N.; Khuwaja, G.; Raza, S.S.; Khan, A.; Javed, H.; Vaibhav, K.; et al. Resveratrol Attenuates 6-Hydroxydopamine-Induced Oxidative Damage and Dopamine Depletion in Rat Model of Parkinson's Disease. *Brain Res.* **2010**, *1328*, 139–151. [CrossRef]
235. Wang, H.; Dong, X.; Liu, Z.; Zhu, S.; Liu, H.; Fan, W.; Hu, Y.; Hu, T.; Yu, Y.; Li, Y.; et al. Resveratrol Suppresses Rotenone-induced Neurotoxicity Through Activation of SIRT1/Akt1 Signaling Pathway. *Anat. Rec.* **2018**, *301*, 1115–1125. [CrossRef]
236. Gao, Z.-B.; Chen, X.-Q.; Hu, G.-Y. Inhibition of Excitatory Synaptic Transmission by Trans-Resveratrol in Rat Hippocampus. *Brain Res.* **2006**, *1111*, 41–47. [CrossRef]
237. Chang, Y.; Wang, S.-J. Inhibitory Effect of Glutamate Release from Rat Cerebrocortical Nerve Terminals by Resveratrol. *Neurochem. Int.* **2009**, *54*, 135–141. [CrossRef]
238. Yáñez, M.; Fraiz, N.; Cano, E.; Orallo, F. Inhibitory Effects of Cis- and Trans-Resveratrol on Noradrenaline and 5-Hydroxytryptamine Uptake and on Monoamine Oxidase Activity. *Biochem. Biophys. Res. Commun.* **2006**, *344*, 688–695. [CrossRef]
239. Sun, W.; Wang, X.; Hou, C.; Yang, L.; Li, H.; Guo, J.; Huo, C.; Wang, M.; Miao, Y.; Liu, J.; et al. Oleuropein Improves Mitochondrial Function to Attenuate Oxidative Stress by Activating the Nrf2 Pathway in the Hypothalamic Paraventricular Nucleus of Spontaneously Hypertensive Rats. *Neuropharmacology* **2017**, *113*, 556–566. [CrossRef] [PubMed]
240. Lange, K.W.; Li, S. Resveratrol, Pterostilbene, and Dementia. *BioFactors* **2018**, *44*, 83–90. [CrossRef] [PubMed]
241. Ader, P. Bioavailability and Metabolism of the Flavonol Quercetin in the Pig. *Free Radic. Biol. Med.* **2000**, *28*, 1056–1067. [CrossRef] [PubMed]
242. Vauzour, D.; Rodriguez-Mateos, A.; Corona, G.; Oruna-Concha, M.J.; Spencer, J.P.E. Polyphenols and Human Health: Prevention of Disease and Mechanisms of Action. *Nutrients* **2010**, *2*, 1106–1131. [CrossRef]
243. Zheng, Q.; Kebede, M.T.; Kemeh, M.M.; Islam, S.; Lee, B.; Bleck, S.D.; Wurfl, L.A.; Lazo, N.D. Inhibition of the Self-Assembly of Aβ and of Tau by Polyphenols: Mechanistic Studies. *Molecules* **2019**, *24*, 2316. [CrossRef]
244. Jaeger, B.N.; Parylak, S.L.; Gage, F.H. Mechanisms of Dietary Flavonoid Action in Neuronal Function and Neuroinflammation. *Mol. Asp. Med.* **2018**, *61*, 50–62. [CrossRef]

245. Van houcke, J.; Mariën, V.; Zandecki, C.; Ayana, R.; Pepermans, E.; Boonen, K.; Seuntjens, E.; Baggerman, G.; Arckens, L. A Short Dasatinib and Quercetin Treatment Is Sufficient to Reinstate Potent Adult Neuroregenesis in the Aged Killifish. *NPJ Regen. Med.* **2023**, *8*, 31. [CrossRef]
246. Wissler Gerdes, E.O.; Misra, A.; Netto, J.M.E.; Tchkonia, T.; Kirkland, J.L. Strategies for Late Phase Preclinical and Early Clinical Trials of Senolytics. *Mech. Ageing Dev.* **2021**, *200*, 111591. [CrossRef]
247. Song, S.; Lam, E.W.F.; Tchkonia, T.; Kirkland, J.L.; Sun, Y. Senescent Cells: Emerging Targets for Human Aging and Age-Related Diseases. *Trends Biochem. Sci.* **2020**, *45*, 578–592. [CrossRef]
248. Hartman, R.E.; Shah, A.; Fagan, A.M.; Schwetye, K.E.; Parsadanian, M.; Schulman, R.N.; Finn, M.B.; Holtzman, D.M. Pomegranate Juice Decreases Amyloid Load and Improves Behavior in a Mouse Model of Alzheimer's Disease. *Neurobiol. Dis.* **2006**, *24*, 506–515. [CrossRef]
249. Ho, L.; Chen, L.H.; Wang, J.; Zhao, W.; Talcott, S.T.; Ono, K.; Teplow, D.; Humala, N.; Cheng, A.; Percival, S.S.; et al. Heterogeneity in Red Wine Polyphenolic Contents Differentially Influences Alzheimer's Disease-Type Neuropathology and Cognitive Deterioration. *J. Alzheimer's Dis.* **2009**, *16*, 59–72. [CrossRef] [PubMed]
250. Mori, T.; Rezai-Zadeh, K.; Koyama, N.; Arendash, G.W.; Yamaguchi, H.; Kakuda, N.; Horikoshi-Sakuraba, Y.; Tan, J.; Town, T. Tannic Acid Is a Natural β-Secretase Inhibitor That Prevents Cognitive Impairment and Mitigates Alzheimer-like Pathology in Transgenic Mice. *J. Biol. Chem.* **2012**, *287*, 6912–6927. [CrossRef] [PubMed]
251. Wang, J.; Ho, L.; Zhao, W.; Ono, K.; Rosensweig, C.; Chen, L.; Humala, N.; Teplow, D.B.; Pasinetti, G.M. Grape-Derived Polyphenolics Prevent A Oligomerization and Attenuate Cognitive Deterioration in a Mouse Model of Alzheimer's Disease. *J. Neurosci.* **2008**, *28*, 6388–6392. [CrossRef]
252. Nugraheni, N.; Ahlina, F.N.; Salsabila, I.A.; Haryanti, S.; Meiyanto, E. Anti-Senescence Activity of Indonesian Black Pepper Essential Oil (*Piper nigrum* L.) on Ovarian CHO-K1 and Fibroblast NIH-3T3 Cells. *Thai J. Pharm. Sci.* **2021**, *45*, 187–194. [CrossRef]
253. Chilelli, N.; Ragazzi, E.; Valentini, R.; Cosma, C.; Ferraresso, S.; Lapolla, A.; Sartore, G. Curcumin and Boswellia Serrata Modulate the Glyco-Oxidative Status and Lipo-Oxidation in Master Athletes. *Nutrients* **2016**, *8*, 745. [CrossRef]
254. Karimian, M.S.; Pirro, M.; Majeed, M.; Sahebkar, A. Curcumin as a Natural Regulator of Monocyte Chemoattractant Protein-1. *Cytokine Growth Factor Rev.* **2017**, *33*, 55–63. [CrossRef]
255. Grabowska, W.; Suszek, M.; Wnuk, M.; Lewinska, A.; Wasiak, E.; Sikora, E.; Bielak-Zmijewska, A. Curcumin Elevates Sirtuin Level but Does Not Postpone in vitro Senescence of Human Cells Building the Vasculature. *Oncotarget* **2016**, *7*, 19201–19213. [CrossRef]
256. Kim, T.; Davis, J.; Zhang, A.J.; He, X.; Mathews, S.T. Curcumin Activates AMPK and Suppresses Gluconeogenic Gene Expression in Hepatoma Cells. *Biochem. Biophys. Res. Commun.* **2009**, *388*, 377–382. [CrossRef]
257. Liu, Z.; Cui, C.; Xu, P.; Dang, R.; Cai, H.; Liao, D.; Yang, M.; Feng, Q.; Yan, X.; Jiang, P. Curcumin Activates AMPK Pathway and Regulates Lipid Metabolism in Rats Following Prolonged Clozapine Exposure. *Front. Neurosci.* **2017**, *11*, 558. [CrossRef]
258. Ray Hamidie, R.D.; Yamada, T.; Ishizawa, R.; Saito, Y.; Masuda, K. Curcumin Treatment Enhances the Effect of Exercise on Mitochondrial Biogenesis in Skeletal Muscle by Increasing CAMP Levels. *Metabolism* **2015**, *64*, 1334–1347. [CrossRef]
259. Juturu, V.; Sahin, K.; Pala, R.; Tuzcu, M.; Ozdemir, O.; Orhan, C.; Sahin, N. Curcumin Prevents Muscle Damage by Regulating NF-KB and Nrf2 Pathways and Improves Performance: An in vivo Model. *J. Inflamm. Res.* **2016**, *9*, 147–154. [CrossRef] [PubMed]
260. Namirah, I.; Wimbanu, K.S.; Rompies, A.M.E.; Prayogo, Y.S.; Arozal, W.; Fadilah, F.; Hanafi, M.; Hardiany, N.S. The Effect of Ethanol-Based Coriander (*Coriandrum sativum* L.) Seed Extract on Oxidative Stress, Antioxidant Level and Cellular Senescence in the Heart of Obese Rat. *J. Pharm. Pharmacogn. Res.* **2024**, *12*, 1111–1120. [CrossRef]
261. Hardiany, N.S.; Dewi, P.K.K.; Dewi, S.; Tejo, B.A. Exploration of Neuroprotective Effect from *Coriandrum sativum* L. Ethanolic Seeds Extracts on Brain of Obese Rats. *Sci. Rep.* **2024**, *14*, 603. [CrossRef]
262. Qin, X.-Y.; Cheng, Y.; Cui, J.; Zhang, Y.; Yu, L.-C. Potential Protection of Curcumin against Amyloid β-Induced Toxicity on Cultured Rat Prefrontal Cortical Neurons. *Neurosci. Lett.* **2009**, *463*, 158–161. [CrossRef]
263. Muthian, G.; Mackey, V.; Prasad, K.; Charlton, C. Curcumin and an Antioxidant Formulation Protect C57BL/6J Mice from MPTP-Induced Parkinson's Disease like Changes: Potential Neuroprotection for Neurodegeneration. *J. Park. Restless Legs Syndr.* **2018**, *8*, 49–59. [CrossRef]
264. Canistro, D.; Chiavaroli, A.; Cicia, D.; Cimino, F.; Curro, D.; Dell Agli, M.; Ferrante, C.; Giovannelli, L.; Leone, S.; Martinelli, G.; et al. The Pharmacological Basis of the Curcumin Nutraceutical Uses: An Update. *Pharmadvances* **2021**, *03*, 421. [CrossRef]
265. Tønnesen, H.H.; Karlsen, J.; Henegouwen, G.B. Studies on Curcumin and Curcuminoids VIII. Photochemical Stability of Curcumin. *Z. Für Lebensm. Unters. Forschung* **1986**, *183*, 116–122. [CrossRef]
266. Huang, W.-T.; Niu, K.-C.; Chang, C.-K.; Lin, M.-T.; Chang, C.-P. Curcumin Inhibits the Increase of Glutamate, Hydroxyl Radicals and PGE2 in the Hypothalamus and Reduces Fever during LPS-Induced Systemic Inflammation in Rabbits. *Eur. J. Pharmacol.* **2008**, *593*, 105–111. [CrossRef]
267. Chaudhri, S.K.; Jain, S. A Systematic Review of Piperine as a Bioavailability Enhancer. *J. Drug Deliv. Ther.* **2023**, *13*, 133–136. [CrossRef]

268. Singh, S.; Jamwal, S.; Kumar, P. Neuroprotective Potential of Quercetin in Combination with Piperine against 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Induced Neurotoxicity. *Neural Regen. Res.* **2017**, *12*, 1137. [CrossRef]
269. El-Demerdash, F.M.; Yousef, M.I.; Radwan, F.M.E. Ameliorating Effect of Curcumin on Sodium Arsenite-Induced Oxidative Damage and Lipid Peroxidation in Different Rat Organs. *Food Chem. Toxicol.* **2009**, *47*, 249–254. [CrossRef] [PubMed]
270. Venkatesan, N.; Punithavathi, D.; Arumugam, V. Curcumin Prevents Adriamycin Nephrotoxicity in Rats. *Br. J. Pharmacol.* **2000**, *129*, 231–234. [CrossRef] [PubMed]
271. Strimpakos, A.S.; Sharma, R.A. Curcumin: Preventive and Therapeutic Properties in Laboratory Studies and Clinical Trials. *Antioxid. Redox Signal.* **2008**, *10*, 511–546. [CrossRef] [PubMed]
272. Ambegaokar, S.S.; Wu, L.; Alamshahi, K.; Lau, J.; Jazayeri, L.; Chan, S.; Khanna, P.; Hsieh, E.; Timiras, P.S. Curcumin Inhibits Dose-Dependently and Time-Dependently Neuroglial Cell Proliferation and Growth. *Neuro Endocrinol. Lett.* **2003**, *24*, 469–473.
273. Kim, G.Y.; Kim, K.H.; Lee, S.H.; Yoon, M.S.; Lee, H.J.; Moon, D.O.; Lee, C.M.; Ahn, S.C.; Park, Y.C.; Park, Y.M. Curcumin Inhibits Immunostimulatory Function of Dendritic Cells: MAPKs and Translocation of NF-KB as Potential Targets. *J. Immunol.* **2005**, *174*, 8116–8124. [CrossRef]
274. Park, S.Y.; Kim, D.S.H.L. Discovery of Natural Products from *Curcuma l Onga* That Protect Cells from Beta-Amyloid Insult: A Drug Discovery Effort against Alzheimer's Disease. *J. Nat. Prod.* **2002**, *65*, 1227–1231. [CrossRef]
275. Jiang, J.; Wang, W.; Sun, Y.J.; Hu, M.; Li, F.; Zhu, D.Y. Neuroprotective Effect of Curcumin on Focal Cerebral Ischemic Rats by Preventing Blood–Brain Barrier Damage. *Eur. J. Pharmacol.* **2007**, *561*, 54–62. [CrossRef]
276. Pagliari, S.; Forcella, M.; Lonati, E.; Sacco, G.; Romaniello, F.; Rovellini, P.; Fusi, P.; Palestini, P.; Campone, L.; Labra, M.; et al. Antioxidant and Anti-Inflammatory Effect of Cinnamon (Cinnamomum Verum J. Presl) Bark Extract after In vitro Digestion Simulation. *Foods* **2023**, *12*, 452. [CrossRef]
277. Moselhy, S.S.; Ali, H.K.H. Hepatoprotective Effect of Cinnamon Extracts against Carbon Tetrachloride Induced Oxidative Stress and Liver Injury in Rats. *Biol. Res.* **2009**, *42*, 93–98. [CrossRef]
278. Gunawardena, D.; Karunaweera, N.; Lee, S.; van Der Kooy, F.; Harman, D.G.; Raju, R.; Bennett, L.; Gyengesi, E.; Sucher, N.J.; Münch, G. Anti-Inflammatory Activity of Cinnamon (C. Zeylanicum and C. Cassia) Extracts—Identification of E-Cinnamaldehyde and o-Methoxy Cinnamaldehyde as the Most Potent Bioactive Compounds. *Food Funct.* **2015**, *6*, 910–919. [CrossRef]
279. Shi, H.; Ge, X.; Ma, X.; Zheng, M.; Cui, X.; Pan, W.; Zheng, P.; Yang, X.; Zhang, P.; Hu, M.; et al. A Fiber-Deprived Diet Causes Cognitive Impairment and Hippocampal Microglia-Mediated Synaptic Loss through the Gut Microbiota and Metabolites. *Microbiome* **2021**, *9*, 223. [CrossRef] [PubMed]
280. Gareau, M.G.; Gareau, M.G.; Lyte, M.; Cryan, J.F. Microbiota-Gut-Brain Axis and Cognitive Function Abbreviations 5-HT Serotonin ANS Autonomic Nervous System BDNF Brain Derived Neurotropic Factor CD Crohn's Disease CREB CAMP Response Element Binding Protein CRF Corticotrophin-Releasing Factor DA Dopamine. *Adv. Exp. Med. Biol.* **2014**, *817*, 357–371. [CrossRef] [PubMed]
281. Unger, M.M.; Spiegel, J.; Dillmann, K.U.; Grundmann, D.; Philippeit, H.; Bürmann, J.; Faßbender, K.; Schwiertz, A.; Schäfer, K.H. Short Chain Fatty Acids and Gut Microbiota Differ between Patients with Parkinson's Disease and Age-Matched Controls. *Park. Relat. Disord.* **2016**, *32*, 66–72. [CrossRef] [PubMed]
282. Martins, I.J.; Fernando, W.M.A.D.B. High Fibre Diets and Alzheimer's Disease. *Food Nutr. Sci.* **2014**, *05*, 410–424. [CrossRef]
283. Den Besten, G.; Van Eunen, K.; Groen, A.K.; Venema, K.; Reijngoud, D.J.; Bakker, B.M. The Role of Short-Chain Fatty Acids in the Interplay between Diet, Gut Microbiota, and Host Energy Metabolism. *J. Lipid Res.* **2013**, *54*, 2325–2340. [CrossRef]
284. Zilberter, Y.; Zilberter, M. The Vicious Circle of Hypometabolism in Neurodegenerative Diseases: Ways and Mechanisms of Metabolic Correction. *J. Neurosci. Res.* **2017**, *95*, 2217–2235. [CrossRef]
285. Erny, D.; Hrabě de Angelis, A.L.; Jaitin, D.; Wieghofer, P.; Staszewski, O.; David, E.; Keren-Shaul, H.; Mahlakoiv, T.; Jakobshagen, K.; Buch, T.; et al. Host Microbiota Constantly Control Maturation and Function of Microglia in the CNS. *Nat. Neurosci.* **2015**, *18*, 965–977. [CrossRef]
286. Wang, J.; Ji, H.; Wang, S.; Liu, H.; Zhang, W.; Zhang, D.; Wang, Y. Probiotic Lactobacillus Plantarum Promotes Intestinal Barrier Function by Strengthening the Epithelium and Modulating Gut Microbiota. *Front. Microbiol.* **2018**, *9*, 1953. [CrossRef]
287. Yi, H.; Wang, L.; Xiong, Y.; Wang, Z.; Qiu, Y.; Wen, X.; Jiang, Z.; Yang, X.; Ma, X. Lactobacillus Reuteri LR1 Improved Expression of Genes of Tight Junction Proteins via the MLCK Pathway in IPEC-1 Cells during Infection with Enterotoxigenic Escherichia Coli K88. *Mediat. Inflamm.* **2018**, *2018*, 6434910. [CrossRef]
288. Perdigón, G.; Maldonado Galdeano, C.; Valdez, J.C.; Medici, M. Interaction of Lactic Acid Bacteria with the Gut Immune System. *Eur. J. Clin. Nutr.* **2002**, *56*, S21–S26. [CrossRef]
289. Toscano, M.; De Grandi, R.; Stronati, L.; De Vecchi, E.; Drago, L. Effect of Lactobacillus Rhamnosus HN001 and Bifidobacterium Longum BB536 on the Healthy Gut Microbiota Composition at Phyla and Species Level: A Preliminary Study. *World J. Gastroenterol.* **2017**, *23*, 2696–2704. [CrossRef] [PubMed]
290. Marotta, A.; Sarno, E.; Del Casale, A.; Pane, M.; Mogna, L.; Amoruso, A.; Felis, G.E.; Fiorio, M. Effects of Probiotics on Cognitive Reactivity, Mood, and Sleep Quality. *Front. Psychiatry* **2019**, *10*, 164. [CrossRef] [PubMed]

291. Sharma, R.; Padwad, Y. Probiotic Bacteria as Modulators of Cellular Senescence: Emerging Concepts and Opportunities. *Gut Microbes* **2020**, *11*, 335–349. [CrossRef]
292. Kechagia, M.; Basoulis, D.; Konstantopoulou, S.; Dimitriadi, D.; Gyftopoulou, K.; Skarmoutsou, N.; Fakiri, E.M. Health Benefits of Probiotics: A Review. *ISRN Nutr.* **2013**, *2013*, 481651. [CrossRef]
293. Azad, F.J.; Talaei, A.; Rafatpanah, H.; Yousefzadeh, H.; Jafari, R.; Jafari, M.; Talaei, A.; Hosseini, R.F.; Jabari, F. Association between cytokine production and disease severity in Alzheimer's disease. *Iran. J. Allergy Asthma Immunol.* **2014**, *13*, 433–439.
294. Eifler, N.; Vetsch, M.; Gregorini, M.; Ringler, P.; Chami, M.; Philippsen, A.; Fritz, A.; Müller, S.A.; Glockshuber, R.; Engel, A.; et al. Cytotoxin ClyA from Escherichia Coli Assembles to a 13-Meric Pore Independent of Its Redox-State. *EMBO J.* **2006**, *25*, 2652–2661. [CrossRef]
295. Gazerani, P. Probiotics for Parkinson's Disease. *Int. J. Mol. Sci.* **2019**, *20*, 4121. [CrossRef]
296. O'Hagan, C.; Li, J.V.; Marchesi, J.R.; Plummer, S.; Garaiova, I.; Good, M.A. Long-Term Multi-Species Lactobacillus and Bifidobacterium Dietary Supplement Enhances Memory and Changes Regional Brain Metabolites in Middle-Aged Rats. *Neurobiol. Learn. Mem.* **2017**, *144*, 36–47. [CrossRef]
297. Distrutti, E.; O'Reilly, J.A.; McDonald, C.; Cipriani, S.; Renga, B.; Lynch, M.A.; Fiorucci, S. Modulation of Intestinal Microbiota by the Probiotic VSL#3 Resets Brain Gene Expression and Ameliorates the Age-Related Deficit in LTP. *PLoS ONE* **2014**, *9*, e106503. [CrossRef]
298. Chandra, S.; Sisodia, S.S.; Vassar, R.J. The Gut Microbiome in Alzheimer's Disease: What We Know and What Remains to Be Explored. *Mol. Neurodegener.* **2023**, *18*, 9. [CrossRef]
299. Mossello, E.; Ballini, E.; Boncinelli, M.; Monami, M.; Lonetto, G.; Mello, A.M.; Tarantini, F.; Baldasseroni, S.; Mannucci, E.; Marchionni, N. Glucagon-like Peptide-1, Diabetes, and Cognitive Decline: Possible Pathophysiological Links and Therapeutic Opportunities. *Exp. Diabetes Res.* **2011**, *2011*, 281674. [CrossRef] [PubMed]
300. Franco-Robles, E.; López, M.G. Implication of Fructans in Health: Immunomodulatory and Antioxidant Mechanisms. *Sci. World J.* **2015**, *2015*, 289267. [CrossRef] [PubMed]
301. Barichella, M.; Pacchetti, C.; Bolliri, C.; Cassani, E.; Iorio, L.; Pusani, C.; Pinelli, G.; Privitera, G.; Cesari, I.; Faierman, S.A.; et al. Probiotics and Prebiotic Fiber for Constipation Associated with Parkinson Disease. *Neurology* **2016**, *87*, 1274–1280. [CrossRef] [PubMed]
302. Ibrahim, A.; Raja Ali, R.A.; Abdul Manaf, M.R.; Ahmad, N.; Tajurruddin, F.W.; Qin, W.Z.; Md Desa, S.H.; Ibrahim, N.M. Multi-Strain Probiotics (Hexbio) Containing MCP BCMC Strains Improved Constipation and Gut Motility in Parkinson's Disease: A Randomised Controlled Trial. *PLoS ONE* **2020**, *15*, e0244680. [CrossRef]
303. Sarparast, M.; Dattmore, D.; Alan, J.; Lee, K.S.S. Cytochrome P450 Metabolism of Polyunsaturated Fatty Acids and Neurodegeneration. *Nutrients* **2020**, *12*, 3523. [CrossRef]
304. Şimşek, H.; Uçar, A. Polyunsaturated Fatty Acids as a Nutraceutical for Age-Related Neurodegenerative Diseases: Current Knowledge and Future Directions. *Clin. Nutr. Open Sci.* **2024**, *56*, 65–73. [CrossRef]
305. Luchtman, D.W.; Song, C. Cognitive Enhancement by Omega-3 Fatty Acids from Child-Hood to Old Age: Findings from Animal and Clinical Studies. *Neuropharmacology* **2013**, *64*, 550–565. [CrossRef]
306. Youdim, K.A.; Martin, A.; Joseph, J.A. Essential Fatty Acids and the Brain: Possible Health Implications. *Int. J. Dev. Neurosci.* **2000**, *18*, 383–399. [CrossRef]
307. Joffre, C.; Dinel, A.L.; Chataigner, M.; Pallet, V.; Layé, S. N-3 Polyunsaturated Fatty Acids and Their Derivates Reduce Neuroinflammation during Aging. *Nutrients* **2020**, *12*, 647. [CrossRef]
308. Uauy, R.; Dangour, A.D. Nutrition in Brain Development and Aging: Role of Essential Fatty Acids. *Nutr. Rev.* **2006**, *64*, S24–S33. [CrossRef]
309. Kerdiles, O.; Layé, S.; Calon, F. Omega-3 Polyunsaturated Fatty Acids and Brain Health: Preclinical Evidence for the Prevention of Neurodegenerative Diseases. *Trends Food Sci. Technol.* **2017**, *69*, 203–213. [CrossRef]
310. Singh, P.K.; Gupta, M.K.; Nath, R. *Omega-3 Fatty Acid as a Protectant in Lead-Induced Neurotoxicity*; Elsevier Inc.: Amsterdam, The Netherlands, 2023; ISBN 9780323900522.
311. Gao, X.; Chen, H.; Fung, T.T.; Logroscino, G.; Schwarzschild, M.A.; Hu, F.B.; Ascherio, A. Prospective Study of Dietary Pattern and Risk of Parkinson Disease. *Am. J. Clin. Nutr.* **2007**, *86*, 1486–1494. [CrossRef] [PubMed]
312. Bousquet, M.; St-Amour, I.; Vandal, M.; Julien, P.; Cicchetti, F.; Calon, F. High-Fat Diet Exacerbates MPTP-Induced Dopaminergic Degeneration in Mice. *Neurobiol. Dis.* **2012**, *45*, 529–538. [CrossRef]
313. Bousquet, M.; Calon, F.; Cicchetti, F. Impact of Omega-3 Fatty Acids in Parkinson's Disease. *Ageing Res. Rev.* **2011**, *10*, 453–463. [CrossRef]
314. Calon, F.; Cicchetti, F. Can We Prevent Parkinson's Disease with n-3 Polyunsaturated Fatty Acids? *Future Lipidol.* **2008**, *3*, 133–137. [CrossRef]

315. Olde Rikkert, M.G.M.; Verhey, F.R.; Blesa, R.; Von Arnim, C.A.F.; Bongers, A.; Harrison, J.; Sijben, J.; Scarpini, E.; Vandewoude, M.F.J.; Vellas, B.; et al. Tolerability and Safety of Souvenaid in Patients with Mild Alzheimer's Disease: Results of Multi-Center, 24-Week, Open-Label Extension Study. *J. Alzheimer's Dis.* **2015**, *44*, 471–480. [CrossRef]
316. Calon, F.; Lim, G.P.; Morihara, T.; Yang, F.; Ubeda, O.; Salem, N.; Frautschy, S.A.; Cole, G.M. Dietary N-3 Polyunsaturated Fatty Acid Depletion Activates Caspases and Decreases NMDA Receptors in the Brain of a Transgenic Mouse Model of Alzheimer's Disease. *Eur. J. Neurosci.* **2005**, *22*, 617–626. [CrossRef]
317. Mangoni, A.A.; Jackson, S.H.D. Age-related Changes in Pharmacokinetics and Pharmacodynamics: Basic Principles and Practical Applications. *Br. J. Clin. Pharmacol.* **2004**, *57*, 6–14. [CrossRef] [PubMed]
318. Sergides, C.; Chirilâ, M.; Silvestro, L.; Pitta, D.; Pittas, A. Bioavailability and Safety Study of Resveratrol 500 Mg Tablets in Healthy Male and Female Volunteers. *Exp. Ther. Med.* **2016**, *11*, 164–170. [CrossRef]
319. Bonassi, S.; Prinzi, G.; Lamonaca, P.; Russo, P.; Paximadas, I.; Rasoni, G.; Rossi, R.; Ruggi, M.; Malandrino, S.; Sánchez-Flores, M.; et al. Clinical and Genomic Safety of Treatment with Ginkgo Biloba L. Leaf Extract (IDN 5933/Ginkgoselect®Plus) in Elderly: A Randomised Placebo-Controlled Clinical Trial [GiBiEx]. *BMC Complement. Altern. Med.* **2018**, *18*, 22. [CrossRef]
320. Soleimani, V.; Sahebkar, A.; Hosseinzadeh, H. Turmeric (Curcuma Longa) and Its Major Constituent (Curcumin) as Nontoxic and Safe Substances: Review. *Phytother. Res.* **2018**, *32*, 985–995. [CrossRef] [PubMed]