

Review Article

Protection from the Pathogenesis of Neurodegenerative Disorders, including Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Huntington's Disease, and Parkinson's Diseases, through the Mitigation of Reactive Oxygen Species

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Keywords: Alzheimer's disease; Amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; Nutrients; Oxidative stress; Reactive oxygen species



Abstract

The biological changes caused by oxidative stress (OS) are known to be involved in the etiology of neurodegenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease. The brain is particularly vulnerable to OS due to its high lipid content and extensive consumption of oxygen. OS processes, particularly the excessive production of reactive oxygen species (ROS), play a critical role in how neurodegenerative disorders develop. This is evidenced by *in vivo* studies investigating various biomolecules related to OS, such as products of lipid and DNA oxidation. Accordingly, ROS can also cause oxidative-related damage in neurodegenerative disorders, including dopamine auto-oxidation, mitochondrial dysfunction, glial cell activation, α -synuclein aggregation, excessive free iron, and changes in calcium signaling. Furthermore, excessive levels of cellular oxidants reduce antioxidant defenses, which in turn propagate the cycle of OS. As such, it is increasingly important to determine the linkage between a high intake of antioxidants through dietary interventions and a lower risk of developing neurodegenerative diseases. Indeed, in addition to modulating the immune system, optimal nutritional status is capable of changing various processes of neuroinflammation known to be involved in the pathogenesis of neurodegeneration. Accordingly, a better understanding of the role ROS plays in the etiology of neurodegeneration is needed, along with the identification of dietary interventions that may lead to improved therapeutic strategies for both the treatment and prevention of neurodegenerative disorders. Therefore, this review presents a comprehensive summary of the role of ROS in the pathogenesis of neurodegenerative disorders. In addition, nutrients believed to be useful for mitigating and counteracting ROS are discussed.

Introduction

In order for the central nervous system (CNS) to function normally, the brain should be free from biochemical impairments [1,2]. Oxidative stress (OS) is one of the main factors that contribute to the biochemical impairment of the brain [3]. Due to its high oxygen consumption and lipid content, the brain is highly susceptible to OS [4,5]. OS stems from an imbalance in the cellular antioxidant response system, which can occur as a result of low dietary antioxidant consumption [6,7]. In particular, OS denotes an imbalance

between the creation of reactive oxygen species (ROS) and the mitigating effects of antioxidants [5]. In turn, excessive cellular oxidant levels are known to reduce antioxidant levels [8]. Accordingly, high oxygen consumption is known to cause extensive ROS production, with the resulting accumulation of ROS contributing to a decline in cellular antioxidants [5,9]. In this review, we emphasize the role of ROS in the pathogenesis of various neurodegenerative diseases, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and Parkinson's disease (PD).



Antioxidant-based treatments are quickly emerging as an encouraging option to delay the progression of neurological diseases [10,11]. Indeed, the consumption of antioxidant-rich foods has been shown to help reduce the extent of oxidative damage caused by free radicals, which are produced during various pathological processes, including amyloid-beta ($A\beta$) accumulation, altered antioxidant defenses, inflammation, and mitochondrial anomalies [12,13]. Accordingly, antioxidant treatments can facilitate neuroprotection by delaying the occurrence or even reversing OS in some cases [14]. In addition, diet is known to play a key role in neurodegenerative diseases, and the development of irreversible neurocognitive decline can be prevented or delayed by the consumption of certain nutrients and appropriate dietary modifications [15,16]. Therefore, nutrients known to be useful in mitigating or counteracting ROS in neurodegenerative disorders will also be discussed.

Oxidative stress and reactive oxygen species

Although oxygen is crucial to life and is involved in numerous biological processes, including gene transcription and signal transduction, it can also have negative impacts on biomolecules via ROS and free radicals [7,17]. The adverse effects of oxygen can be attributed to its univalent metabolic reduction status, which leads to the development of ROS [9]. The accumulation of ROS results in a cellular state of OS, which is defined as an imbalance between a biological system's oxidant and antioxidant levels [18]. This imbalance can be caused by excessive levels of ROS or dysfunction in the cellular antioxidant system [19,20].

Free radicals refer to molecular fragments that contain at least one unpaired electron in their respective molecular/atomic orbitals [21]. These unpaired electron(s) provide free radicals with copious amounts of reactivity, with oxygen free radicals representing the most significant category of radical species in living organisms [22]. In general, the production of oxygen free radicals occurs during reactions associated with cellular metabolism [18]. Indeed, during the transduction of energy, a limited number of electrons end up leaking prematurely to oxygen for the generation of superoxide ($O_2^{\cdot-}$) [23]. In addition, during periods of OS, excessive amounts of $O_2^{\cdot-}$ serve to expel iron from iron-containing molecules, leading to the generation of the extremely reactive hydroxyl radical ($\cdot OH$) through the Fenton reaction [22]. As a result, the formation of additional reactive radicals can occur, including the generation of peroxy radicals [17]. The perhydroxyl radical, otherwise known as the hydroperoxyl radical, is considered the simplest of such radical. Hydroperoxyl radicals can initiate the peroxidation of fatty acids [17]. In addition, $O_2^{\cdot-}$ can swiftly react with NO to generate peroxynitrite, which is a reactive nitrogen species (RNS) that can inflict significant damage to intracellular components [18,24]. In this manner, the term ROS is inclusive of $\cdot OH$, $O_2^{\cdot-}$, and hydrogen peroxide (H_2O_2) [21,25].

Oxidative damage

ROS can cause serious harm to macromolecules, including nucleic acids, lipids, proteins, and polysaccharides [4,6,26]. In terms of the CNS, certain properties of neurons make them particularly susceptible to the deleterious effects of ROS. These properties include a composition of fatty acids that is vulnerable to peroxidation, high rates of metabolism, heightened concentrations of transition metals, low antioxidant levels, and a lower regenerative capacity [22].

In addition, neurons experience intense demands related to energy, with the mitochondria both an important source and target of ROS [27]. OS is also known to stimulate mitochondrial fission [28]. This is evidenced by studies wherein H_2O_2 is added onto cultured cerebellar granule neurons, which induces mitochondrial fragmentation within an hour of treatment [29].

OS can also lead to alterations in the structure of proteins, and impaired protein structures can further exacerbate oxidative damage [9]. Indeed, ROS causes protein oxidation and modified protein structures that easily aggregate and dimerize [30]. These functionally and structurally abnormal oxidized proteins then accumulate within the cytoplasm of neurons in the form of $A\beta$ plaques and tau neural fibrillary tangles (NFT) [31]. $A\beta$ plaques themselves are also known to be responsible for the formation of ROS, resulting in a continuous cycle of OS [30]. In addition, a growing body of evidence has demonstrated that ROS causes oxidative damage to lipids and DNA, which leads to various cellular dysfunctions [4,32,33]. In summary, oxidative damage is inclusive of dopamine auto-oxidation, mitochondrial dysfunction, glial cell activation, α -synuclein aggregation, changes in calcium signaling, and excessive free iron [34–36].

Oxidative stress and neurodegenerative disorders

Sustained oxidative stress, in particular, ROS may also trigger abnormalities in mitochondrial function, impairment of the DNA repair system, and cellular damage, all of which are considered to play decisive roles in accelerating the aging process and the development of neurodegenerative disorders [37,38]. Indeed, a large body of evidence exists underscoring the role of ROS in several human disease states, including neurodegenerative disorders [39–42]. Therefore, continued efforts are critical to identifying agents that could be potentially useful in the treatment and prevention of neurodegenerative diseases [7,43]. Many studies have observed the association between the accumulation of ROS and the pathogenesis of neurodegenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's diseases [39–41,44]. In brief, Alzheimer's disease is a neurodegenerative disorder that is characterized by the progressive loss of memory and the development of dementia [45,46], whereas Huntington's disease refers to a hereditary disorder of the CNS [40,42]. The symptoms of Huntington's disease include cognitive impairments, movement disorders,



and psychiatric disorders [47]. Amyotrophic lateral sclerosis is a serious neuromuscular disorder characterized by the loss of motor neurons and significant skeletal muscle wasting over a short period of time [48].

In contrast, Parkinson's disease is considered a long-term, progressive age-related neurodegenerative disease characterized by motor dysfunction [49,50].

Alzheimer's Disease (AD)

Alzheimer disease is a brain-specific disorder characterized by the presence of tau NFT, neural inflammation, and A β plaques [51-53]. These pathologies cause neuronal death and concomitant clinical symptoms, such as confusion, impaired cognitive function, and memory loss [54-56]. One of the key characteristics of AD is the substantial and progressive erosion of neurons in the cortex [57]. Indeed, maximal degeneration takes place in the cortex and hippocampus, which leads to deficiencies in both learning and memory [58]. Typically, AD symptoms commence with mild amnesia and confusion, eventually leading to radical changes in the personality of the afflicted individual [59]. Other AD signs include vision/spatial abnormalities, poor word recall, and deficits in judgment or reasoning [59].

Alzheimer's disease and oxidative stress

An imbalance between ROS production and the activities of enzymes responsible for ROS scavenging results in increased oxidative damage in AD patients [54]. Numerous studies have demonstrated that OS and ROS have a significant role in AD by causing deleterious effects to proteins and other important biomolecules [20,60]. ROS oxidize β -amyloid and tau, and the resulting oxidative imbalance leads to further neuronal damage

in AD patients [61,62]. These oxidized proteins accumulate in the cytoplasm of neurons to create A β plaques, which serve to propagate the cycle of oxidative damage via increasing ROS levels [63,64]. Another contribution of OS to AD is through mitochondrial dysfunction caused by the accumulation of the A β aggregates [54]. In this regard, mitochondrial dysfunction is a key protagonist in the pathogenesis of AD [12,65,66]. In particular, mitochondrial dysfunction is caused by a number of factors, including oxidative stress from the generation of ROS, membrane damage, mitochondrial damage (DNA-related), the destabilization of ionic gradients, and interactions with A β , which is regarded as a toxic protein [67,68]. According to emerging evidence, there may be an association between tau pathology and OS [69,70]. Indeed, cells containing overexpressed tau proteins appear to be particularly vulnerable to OS [71]. In summary, amyloid plaque, Tau aggregation, excessive generation of ROS, mitochondrial dysfunction, accumulation of Iron and impaired calcium homeostasis, and poor antioxidant status generates oxidative stress, particularly ROS in AD. Enhanced oxidative alterations to β -amyloid protein lead to protein misfolding and protein aggregation which in turn causes exacerbation of neurodegeneration and death of neuronal cells in AD [22]. The destruction of the cells leads to brain atrophy in AD.

Alzheimer's disease and nutrients

Bioactive nutrients are believed to be some of the few factors that are effective in AD (Table 1) [72]. A growing body of evidence indicates that a wholesome dietary plan consisting of fish, fruit, and vegetables is important for optimizing cognition and reducing the risk of AD [73]. In particular, reduced levels of fat-soluble vitamins, such as vitamins A, D, E, and K, may be responsible for causing a cognitive decline among AD

Table 1: Summary of nutraceuticals suggested for prevention and therapy of neurodegenerative diseases.

Nutraceuticals	Beneficial Effects	Mechanism	Support for Diseases
Vitamin E	Antioxidant, Neuroprotection	Vitamin E is a scavenger of several ROS and serves to reduce their reactivity and toxicity. It offers protection from the propagative damage of ROS by inhibiting the oxidative modification of lipoproteins	AD [74-79,82-86] PD [175-177,79] ALS [193,217,218]
Vitamin C	Antioxidant, Neuroprotection	Vitamin C is an excellent antioxidant, suitable in reducing ROS levels, lipid peroxidation, and oxidative stress. It is also useful in regenerating other antioxidants.	AD [81,82,75,77,79] PD [166-168] ALS [213,214]
Vitamin D	Antioxidant Neuroprotection	Vitamin D prevent oxidative stress, lower the production of free radicals, and reduce neurotoxicity through the enhancement of autophagy signaling pathways	AD [74-78,30,16,80] PD [157-159,169-174] ALS [215,216]
Vitamin A	Antioxidant	Vitamin A prevent the formation of A β plaques	AD [16,30,74-78]
Vitamin B	Antioxidant Neuroprotection	Vitamin B perform antioxidant and neuroprotective functions	AD [88-90] PD [157-159,162-165] HD [105]
Curcumin	Antioxidant Anti-inflammatory Neuroprotection	Curcumin is a scavenger of free radicals and reduces mitochondrial dysfunction.	AD [100,101]
Omega-3 fatty acids	Antioxidant Anti-inflammatory	Omega-3 fatty acids reduce ROS formation acting as free radical scavengers.	AD [92-94] PD [175,180-182] ALS [193,217]
Flavonoids	Antioxidant Anti-inflammatory Neuroprotection Neuromodulation	Flavonoids scavenge ROS and acts as antioxidative, antiapoptotic, and anti-inflammatory agent.	AD [95-97]. PD [97,185-188]
Polyphenols	Antioxidant, Anti-inflammatory, Anti-apoptotic	Polyphenols reduces the levels of A β and offers antioxidant, anti-inflammatory, mitochondrial protective, and anti-apoptotic activities.	AD [95-97] HD [42,43,95, 125] PD [95,183,184]



patients [30,74-76]. Antioxidants that may help treat AD as adjuvants to traditional therapies include vitamins A, C, and E [16,30,75,77]. Vitamin A has been reported to prevent the formation of A β plaques [78]. In addition, vitamins C and E have also proven to be beneficial in delaying or preventing the progression to irreversible neurocognitive decline [79]. Furthermore, higher consumption of vitamin D is associated with a lower risk of AD [80].

Studies have suggested that vitamin C may be able to halt the development of AD due to its role in mitigating various processes associated with AD pathology [81]. Both *in vitro* and *in vivo* studies have reported that vitamin C helps reduce OS by impeding A β oligomerization [11,15]. Damage to the brain leads to a decline in antioxidants and important enzymes, including vitamin C and superoxide dismutase (SOD), which neutralizes O $_2^{\cdot-}$ radicals [81]. Vitamin C itself can help increase SOD levels and decrease levels of associated OS [81]. Indeed, researchers have postulated that even a normal vitamin C intake through diet can exert a neuroprotective effect among AD patients [30]. A study of 4,740 participants showed that an intake of vitamins E and C for at least three years reduced the risk of developing AD [82]. Vitamin E is considered to be an important antioxidant micronutrient, and studies have shown that vitamin E can safeguard cells from oxidative damage [75,83]. In addition, vitamin E offers protection from the propagative damage of ROS by inhibiting the oxidative modification of lipoproteins [84,85]. Indeed, a study comprising 904 patients with AD and 1,153 healthy older controls confirmed that serum vitamin E levels were lower in the AD patients compared with the controls [86]. In this regard, an increased intake of quality dairy, fresh fruit, vegetables, fish, and whole grains, along with the reduced consumption of fried potatoes, sweets, and processed meat, may provide an efficacious nutrient combination and offer protection against AD [84,87].

In addition, various B vitamins, including folate (or B $_9$), B $_6$, and B $_{12}$, have been reported to have a positive impact on AD patients in terms of their influence on the metabolism of homocysteine, which is a sulfur amino acid source derived from the metabolism of methionine [88-90]. In addition, magnesium, inositol, choline, B $_1$, isoflavones, and anthocyanins may help prevent the development of AD [91]. In addition, dietary omega-3 fatty acids are also known to improve the functioning of the brain in a similar manner [92,93]. A study comprising 815 participants between the ages of 65 and 94 found a 60% lower risk of developing AD in those who consumed fish at least once per week [94].

A growing body of evidence suggests that polyphenols and flavonoids scavenge RNS and ROS, thus playing an important beneficial role in patients suffering from degenerative diseases related to aging [95-97]. Polyphenols are key antioxidant substances found in abundant quantities in various fruits, such as grapes, blueberries, and tomatoes, vegetables, olive

oil, spices, herbs, and certain beverages such as tea and coffee [95,96,98,99]. In AD, polyphenols may reduce the levels of A β [95,96]. Curcumin is derived from the turmeric root and is considered a beneficial polyphenol with strong antioxidant properties; reports have indicated that curcumin may have benefits in several degenerative diseases relating to aging, such as AD [100,101]. Since polyphenols and flavonoids are found in fruits and vegetables, the daily consumption of a healthy diet is considered a useful preventive approach against neurodegenerative disorders [102]. Similarly, nuts, including walnuts, almonds, and hazelnuts, offer essential phytochemicals and micronutrients/macronutrients, which can have a positive impact on AD pathogenesis, including processes involving tau phosphorylation, amyloidogenesis, cholinergic pathways, and OS [103].

Huntington's Disease (HD)

Huntington's disease is a genetic neurodegenerative disorder characterized by the selective degeneration of neurons. This degeneration results in progressive disabilities, including motor dysfunction and both cognitive and psychiatric deficiencies [104-106]. HD is associated with polyglutamine-expansion; thus, the disease primarily impacts the cerebral cortex and striatum [107,108]. Key symptoms include motor dysfunction, progressive cognitive decline, and psychiatric disturbances [109,110]. Primarily, HD is known to impact the corpus striatum and is characterized by cognitive/motor deficits and unusual involuntary movements [111,112].

Huntington's disease and oxidative stress

Huntington's disease is caused by a repeat expansion of cytosine-adenine-guanine (CAG) in the huntingtin gene [105,113,114]. The mutant huntingtin protein (mHTT) leads to neuronal dysfunction before ultimately causing cell death due to excitotoxicity, transcriptional deficiencies, inflammation, oxidative damage, mitochondrial dysfunction, and apoptosis [112,115,116]. Excessive mHTT accumulation is responsible for causing an unusually high production of ROS, along with the concomitant mitochondrial OS, in neurons [40,117]. According to several reports, neuronal degeneration mediated by mitochondrial dysfunction and OS is a major contributing factor in HD [107,118]. In addition, OS promulgates mHTT aggregation and cell death by replicating proteasomal abnormalities [119,120]. The heightened production of free radicals also inhibits the production of energy and proper mitochondrial function. Similarly, impairments in metabolism have been shown to cause excitotoxic damage [121]. In HD, oxidative damage has been observed in proteins, lipids, and DNA [122]. In this regard, the inadequate repair of damaged DNA is believed to be a primary contributing factor to the repeat expansion of CAG [123]. In addition, HD patients have been reported to have increased levels of OS markers, along with a decrease in antioxidant status compared with healthy participants [124]. In summary, accumulation of mHTT protein,

impairment in the electron transport chain and mitochondrial dysfunction, imbalance in oxidant-antioxidant status, higher lipid concentration and high energy requirement, and poor antioxidant status generates oxidative stress, particularly ROS in HD. Enhanced oxidative alterations to mHTT protein leads to protein misfolding and protein aggregation which in turn causes exacerbation of neurodegeneration in HD.

Huntington's disease and nutrients

According to various studies (Table 1), vitamin B₅ deficiency may cause dementia and neurodegeneration in HD patients, and treatments that include B₅ may help prevent the progression of HD [105]. Plant-derived polyphenols are ubiquitous compounds characterized by numerous pharmacological properties, including antioxidant, anti-inflammatory, mitochondrial protective, and anti-apoptotic activities [95,42]. Polyphenols are also known to improve cognitive function and delay and/or prevent the onset of certain neurodegenerative diseases, including HD [43,125]. In rodents, olive oil has been shown to decrease oxidative damage in 3-nitropropionic acid-induced HD cases [126]. Studies showed that both hydroxytyrosol and extra virgin olive oil acted as robust brain antioxidants [127]. In addition, other studies have reported that green tea plays a role in preventing early-stage events associated with HD pathogenesis, including Huntington's misfolding [128,129]. Similarly, the combination of fish oil and quercetin has been reported to offer protection against HD induced by 3-nitropropionic acid [130].

Parkinson's disease

Parkinson's disease is a progressive disorder characterized by various motor-related symptoms, including slow movements, body tremors, and rigidity [131,132]. In general, motor symptoms related to PD first manifest after the death of over 60% of dopaminergic neurons within the brain [133,134]. Indeed, the pathological hallmarks of PD include the generation of Lewy bodies and the erosion of dopaminergic neurons in the substantia nigra pars compacta [135-137]. According to a growing body of evidence, neuroinflammation plays a significant role in the pathogenesis of PD, which could serve as a target of neuroprotection [138,139]. Products of dopamine quinones and oxidation also reportedly lead to PD-related neurodegeneration [140,141]. Various exogenous causes have been implicated in the etiology of PD, including the excessive use of pesticides/herbicides, exposure to carbon disulfide and monoxide, plant-derived toxins, and both viral and bacterial infections [20]. In addition, aging appears to be a factor, ceasing the normal cellular processes which in turn leading to the increased degeneration of dopaminergic neurons [142].

Parkinson's disease and oxidative stress

Oxidative stress and mitochondrial dysfunction play an important role in exacerbating PD [143-146]. Indeed, cellular inflammation and stress are known to cause reactive astrogliosis, which in turn leads to the generation of astrocytic

ROS [147]. In this context, ROS are regarded as important modulators of PD [148,149]. At the same time, dopaminergic neurons of the substantia nigra are especially susceptible to processes of degeneration in PD [141,150]. In addition, increased levels of oxidized proteins and lipids have been observed in PD patients [19]. It is notable that among the organelles capable of generating ROS, mitochondria account for over 90% of all ROS production [151]. During their lifespan, dopamine neurons are constantly exposed to RNS and ROS from metabolic processes localized to the cytosol [152-154]. Being a comparatively unstable molecule, dopamine itself can produce ROS by undergoing auto-oxidation within the nigrostriatal tract system, indicating that oxidation may progress with aging [155,156]. In summary, accumulation of alpha-synuclein protein, impaired respiratory chain and somatic mitochondrial DNA mutations, iron accumulation, enhanced dopamine metabolism, increase in malondialdehyde and hydroperoxides in the substantia nigra, hydroxyl radical accumulation, and poor antioxidant status generates oxidative stress, particularly ROS in PD. Enhanced oxidative alterations to α -synuclein protein lead to protein misfolding and protein aggregation which in turn causes exacerbation of neurodegeneration and destruction of neuronal cells and death of dopaminergic neurons in PD [22]. The destruction of the cells and the reduced dopaminergic transmission in the substantia nigra leads to progressive loss of muscular coordination and balance in PD.

Parkinson's disease and nutrients

It has been reported that PD can be effectively managed with nutritional supplementation, particularly dietary interventions involving foods containing vitamins B and D, as well as coenzyme Q and omega-3 fatty acids (Table 1) [157-159]. Foods that have been established to reduce the progression rate of PD include fresh fruits and vegetables, nuts and seeds, olive oil, fish (non-fried), spices, fresh herbs, and coconut oil [160]. In contrast, foods associated with faster PD progression include fried foods, both non-diet and diet soda, ice cream, beef, cheese, canned fruits/vegetables, and yogurt [160]. Unlike iron supplements, nutritional supplements containing coenzyme Q10 and fish oil have been linked to a lower progression of PD [160]. In addition, tea intake has been linked to a lower risk of developing PD. Indeed, it has been reported that people who consume at least one cup of black tea daily have a decreased risk of developing PD [161].

A deficiency in vitamin B₁₂ is also known to be a key factor that causes comorbidity among PD patients owing to the heightened rate of bacterial overgrowth that occurs in the intestines of 25%–54% of PD patients [90,162,163]. Notably, vitamin B₁₂ is primarily sourced from animals [98]. In one study of 72 PD patients, with a follow-up period of nine years, higher consumption of vitamin B₆ was linked to a considerably decreased risk of PD progression [88]. Furthermore, the B vitamin, niacin (vitamin B₃), is known to lower oxidative stress.



Given that PD pathophysiology is associated with a failure of cellular energy and mitochondrial dysfunction, niacin may perform antioxidant and neuroprotective functions at low doses owing to its role in several metabolic pathways [164,165]. Sources of B vitamins include whole grains, legumes, bananas, meat, and potatoes [98].

Vitamin C also plays a key role in decreasing ROS and lipid peroxidation, in addition to being instrumental for the regeneration of other key antioxidants [166,167]. A study comprising 1,000 PD patients found that the intake of vitamin C decreased the risk of PD progression [168]. Primary sources of vitamin C include fruits, paprika, citrus foods, and vegetables [98]. In addition, multiple clinical studies have reported that concentrations of serum vitamin D are negatively correlated with the severity and risk of PD [169,170]. Vitamin D₃ is known to prevent oxidative stress, lower the production of free radicals, and reduce neurotoxicity through the enhancement of autophagy signaling pathways, thereby having a positive effect in PD patients [171-173]. One study consisting of 2,866 patients with Parkinson's disease and 2,734 healthy controls observed that increased serum vitamin D levels reduced the severity of progression of PD [174]. A regular intake of foods rich in vitamin E may also defer the development or even lower the risk of PD [175]. In fact, vitamin E is a scavenger of several ROS and serves to reduce their reactivity and toxicity [79,175-177]. A study that administered a combination of vitamins C and E to patients in the early stages of PD found that the vitamin regimen slowed the progression of PD [178].

Increased polyunsaturated fatty acids (PUFAs) consumption is inversely correlated with PD [179]. Omega-3 fatty acids act as free radical scavengers and reduce ROS formation [180]. They also decrease the chemotaxis of monocytes and neutrophils and curb the formation of pro-inflammatory cytokines [175,181,182]. A cohort study consisting of 5,000 individuals found that a high intake of omega-3 fatty acids reduced the risk of PD [180]. The sources of Omega-3 fatty acids include fish oils, cold-water fish, flaxseed oil, walnuts, edible seeds, and other dietary supplements [98]. On the other hand, polyphenols demonstrate powerful anti-inflammatory and antioxidant properties [95]. Considering the role of OS and inflammation in the onset and progression of PD, it has been found that dietary polyphenols such as catechins, anthocyanins, resveratrol, theaflavins, and curcumin may offer significant therapeutic benefit in PD [183,184]. Owing to their biological impacts, including as antioxidative, antiapoptotic, and anti-inflammatory agents, as well as their lipid-reducing traits, flavonoids may impart a wide range of health benefits, including diminished risk of PD [97,185-187]. A study of 130,000 participants showed that a high intake of flavonoids reduced the risk of PD [188]. Common flavonoid sources include berries, onions, parsley, all citrus fruits, dark chocolate, red wine, green/black tea, and Ginkgo biloba [189].

In addition, several preclinical studies involving animals

have demonstrated the advantages of probiotics in preventing and treating disorders of the CNS [190]. A study comprising 60 PD patients that were administered a daily probiotic for 12 weeks found that the probiotic reduced the risk of PD progression [191]. In this regard, supplementation, involving probiotics, has shown a wide range of positive impacts on metabolic profiles/symptoms, thereby having the potential to significantly benefit PD patients [191]. Foods with high prebiotic content include artichokes, bamboo shoots, asparagus, bananas, barley, black pepper, chicory coffee, dark beets, chocolate, broccoli, fennel root, endive, mustard greens, Jerusalem artichokes, ginger, jicama, tomatoes, yacón, leeks, and legumes [98].

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis is an irreversible neurodegenerative disorder that quickly progresses and causes the erosion of motor neurons not only within the brain but also throughout the spinal cord [192-194]. In addition, ALS is accompanied by the reduction and dysfunction of upper motor neurons [48,195,196]. ALS leads to the progressive but selective erosion of spinal, bulbar, and cortical motoneurons, which results in speech loss, progressive paralysis, difficulty in swallowing, and several respiratory malfunctions. Ultimately, ALS is fatal, and the time to death is related to the rate of progression [197,198]. As with other neurodegenerative disorders, neuroinflammation is frequently found in ALS [199]. ALS is characterized by inflammation related to astroglia/microglia, macrophages, and pro-inflammatory peripheral lymphocytes [200]. Evidence has shown that several genetic mutations are associated with ALS and amplify this neuroinflammation, which is evidence for immune dysregulation in ALS pathogenesis [199,201].

ALS and oxidative stress

It has been discovered that ALS patients have mutations in the gene encoding the antioxidant enzyme superoxide dismutase 1 (SOD1) [202]. Mutant SOD1 leads to aggregation in motor neurons within the CNS [193]. Other causes include oxidative stress, neuroinflammation, glutamate excitotoxicity, changes in neurofilaments, mitochondrial degeneration and damage, protein aggregation, apoptosis, and deficiencies in factors related to growth [46,203-205]. Owing to the accumulation of dysfunctional mitochondria within the motor neurons impacted by the sporadic and genetic types of ALS, there is a clear indication that a failure to maintain healthy mitochondria exacerbates ALS [206,207]. Among ALS patients, OS has been linked to the degeneration of skeletal muscles and motor neurons [208,209]. Indeed, in conjunction with mitochondrial dysfunction, ROS is considered a major cause of ALS. It is also noteworthy that OS not only raises overall RNS/ROS formation but also impacts the structure and conformation of various proteins, which then causes abnormal protein accumulation [210]. Oxidative stress biomarkers in CNS regions of paramount significance in the context of ALS are also indicative of their involvement in the degeneration

of motor neurons [211]. Mitochondrial dysfunction associated with ALS is known to manifest in numerous ways, including as defective oxidative phosphorylation, ROS production, deficient calcium buffering, and problematic mitochondria dynamics [211]. Moreover, barring the issue of RNA toxicity, mitochondrial dysfunction appears to be correlated with all mechanisms of the toxicity characterizing ALS, such as deficient axonal transport, the erosion of homeostasis, and excitotoxicity [211]. Heightened levels of damage associated with ROS and RNS have been observed in ALS [210]. In addition, increased levels of ROS have been reported in the lymphoblasts of familial cases of ALS [212]. In summary, glutamate-induced excitotoxicity, mitochondrial dysfunction generates oxidative stress, particularly ROS in ALS. Enhanced oxidative alterations to SOD 1 protein lead to protein misfolding and protein degradation which in turn causes exacerbation of neurodegeneration in ALS [22]. The destruction of motor neurons leads to the muscle weakness in ALS.

ALS and nutrients

A higher intake of vegetables and fruits is negatively correlated with ALS [213]. In addition to being an efficacious scavenger of free radicals, vitamin C also modulates the metabolism of neurons by lowering the consumption of glucose during glutamatergic synaptic activity, while also fostering an increase of neuronal lactate, which is consistent with the reduced ratio of lactate to pyruvate observed in ALS patients (Table 1) [214]. A study in rodents administered with vitamin C before and after the onset of ALS found that the former regimen resulted in longer survival by 62% [215]. It has also been demonstrated that vitamin D can affect several facets of the pathology of ALS [216], including reducing the expression of biomarkers linked with neuroinflammation and OS [217].

Fiber, vitamin E, and omega-3 fatty acids can also potentially impart lasting benefits in ALS [193]. A study comprising 132 ALS patients and 220 healthy controls showed that high consumption of vitamin E, in conjunction with omega-3 fatty acids, reduced the risk of developing ALS by as much as 50%–60% [218]. Indeed, the results another study indicated that the participants who consumed vitamin E supplements had a significantly lower risk of death caused by ALS than those who did not, thus underscoring the potential efficacy of vitamin E in the prevention of ALS [219]. In addition, zinc is also known to perform key functions in various pathological mechanisms traditionally correlated with ALS [220]. Cannabinoids have also been postulated as therapeutic options for ALS owing to their anti-inflammatory, antioxidant, and anti-excitotoxicity properties [221,222]. Cannabinoid sources include flax seeds, hemp oil, seeds, eggs, and anchovies [223].

Neurodegenerative disorders and nutraceuticals

The following table 1 displays the beneficial effects and the mechanisms of the nutraceuticals suggested for prevention and treatment of neurodegenerative diseases.

Conclusion

Although major neurodegenerative disorders such as AD, HD, PD, and ALS are linked to multiple pathophysiologic processes as well as etiologies, it is evident that OS and, in particular, the production of ROS, are significant factors. In general, a proper balance between antioxidants and ROS is necessary for cells to function properly, and OS has been attributed to neuroinflammation, dopamine degeneration, and mitochondria dysfunction. Meanwhile, the onset of OS generates ROS, which can have damaging impacts on the neurons within the brain, resulting in neurodegeneration. Similarly, mitochondrial dysfunction has been found to exacerbate the imbalance between antioxidants and ROS within the cellular environment. The excess ROS production leads to neurodegenerative disorders. Enhanced oxidative alterations to β -amyloid proteins in AD, α -synuclein proteins in PD, mHTT proteins in HD, and SOD 1 proteins in ALS lead to protein misfolding and protein aggregation which in turn causes exacerbation of neurodegeneration and destruction of neuronal cells. Given that OS can begin at a young age, the role of dietary intervention assumes great importance in preventing or deferring the advancement of neurodegenerative disorders. Indeed, increasing evidence has shown that antioxidants constitute a promising approach to prevent the occurrence of neurodegenerative diseases. Intake of balanced nutrients and efficient antioxidants may also facilitate the treatment strategies for patients of Alzheimer's disease, Huntington's disease, Parkinson's disease, Amyotrophic lateral sclerosis diseases, and other neurodegenerative diseases.

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