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# DIETARY INTERVENTIONS IN NEURODEGENERATIVE DISEASES: A COMPREHENSIVE REVIEW OF CURRENT RESEARCH AND FUTURE PROSPECTS

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**ABSTRACT**

Neurological disorders represent one of the most considerable global health challenges—affecting approximately one in three people over their lifetimes. As of 2021, ≈ 43% of the global population were living with some form of neurological condition, including stroke, migraine, dementia, and neurodegenerative disorders. Diseases such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis pose significant challenges, as the global population ages. While these conditions are influenced by multifactorial interactions, dietary factors play a crucial role in their onset and progression. Studies show that adherence to the Mediterranean and ketogenic diets along with the supplementation of antioxidants and certain vitamins, can improve memory and cognitive function. The impacts of diet are evidenced by the outcomes of behavioral tests, particularly those assessing motor and cognitive functions, as well as through histopathological and immunohistochemical analyses that indicate the protection of neurons. Further studies have analyzed mechanisms through dietary components modulate oxidative stress, neuroinflammation, iron management in cells, and various signaling pathways. Crucially, understanding the mechanisms of these components is vital for supporting their dietary inclusion in neuroprotective strategies and pinpointing new therapeutic targets in the treatment of neurodegenerative diseases. In this review, the therapeutic mechanisms of diet are discussed in-depth.

Keywords: Antioxidants, Ketogenic Diet, Mediterranean Diet, Neurodegenerative Diseases, Nutrition

## 1. INTRODUCTION

Neurodegeneration is defined as the progressive loss of specific neuronal populations (e.g., cholinergic, dopaminergic), deterioration of local neural microcircuits, and disruption of large-scale brain networks responsible for cognition, motor control, and memory [1,2]. These changes are driven by several interrelated anatomical and physiological factors, including oxidative stress-induced production of reactive oxygen species (ROS), mitochondrial dysfunction, chronic neuroinflammation mediated by microglial activation, excitotoxicity due to excessive glutamate signalling, and protein aggregation involving misfolded proteins such as amyloid-beta, tau, and alpha-synuclein [3–5]. These complex pathological pathways collectively contribute to neuronal impairment and death in various neurodegenerative diseases.
Neurodegenerative diseases are multifactorial enfeebling disorders, comprising a link between genetic predisposition and environmental factors [6]. Neurodegenerative diseases are an increasing cause of mortality and morbidity worldwide, especially with the increase in life expectancy [7]. Despite the clinical manifestations and underlying pathophysiological processes of various neurodegenerative diseases differ, they generally share common features [8]. A certain subsumption of neurodegeneration may be based on the presence of abnormal protein accumulation in the brain, leading to neuronal loss [9]. Various diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are described as aging-brain-related neurodegenerative diseases [10–13]. These neurodegenerative diseases are characterized by loss of cholinergic conduction (acetylcholinesterase (AChE) enzyme increase), apoptosis, and neuronal damage that can be caused by inflammation [14]. In addition, different neurodegenerative diseases including spinal muscular atrophy (SMA) and multiple sclerosis (MS) cause muscular disorders with various mechanisms in the central nervous system [15,16]. Albeit the progression of neurodegenerative diseases can be restrictedly measured through anthropometric, habit, and

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clinical factors, the underlying mechanisms of disorder progression are not completely understood [17]. Although treatments can help alleviate some of the physical and cognitive symptoms of neurodegenerative diseases, it is currently not possible to completely stop disease progression.

Donnan et al. (2008) reported that people with a low-risk and healthy lifestyle (non-smoker, steady exerciser, moderate alcohol drinker, and moderately weight) showed a significantly lower risk of the onset of neurodegenerative diseases compared to the high-risk lifestyle group. Thus, this higher incidence of neurodegenerative diseases may be due to the adverse impact of daily risk factors including lack of exercise, smoking, alcoholism, stress, high levels of LDL cholesterol in plasma, hypertension, physical inactivity, obesity and insufficient nutrition [17].

Several intrinsic elements such as aging, brain injury and related excessive neuroinflammation, OS, and high-calorie diets negatively influence neurodegeneration. However, several specific diets and nutrients may lead to a healthier life and reduce disease symptoms [19]. The recognition of these factors that may decelerate neurodegeneration or even prevent linked diseases is critical for disease precautions. Nutrition is an adjustable parameter that has been associated with neurodegenerative diseases at different levels, including the consumption of specific foods and dietary patterns or intake of certain nutrients [20–22]. In view of the multiple biological interactions between elements in a diet, it was suggested that whole-diet consumption and the use of certain regimen may provide benefits in understanding the role of diet in chronic disorders such as neurodegenerative diseases [23]. This review focuses on the link between diet and selected neurodegenerative diseases

## 2. METHODOLOGY

Data collection was performed by examining sources from Web of Sciences, PubMed, and Scopus databases. The research utilized key phrases including “neurodegenerative diseases”, “neurodegenerative diseases and diet”, "Alzheimer’s disease", Alzheimer’s disease and diet", “Parkinson’s disease”, “Parkinson’s disease and diet”, “Huntington’s disease”, “Huntington’s disease and diet”, “amyotrophic lateral sclerosis”, “amyotrophic lateral sclerosis and diet”, “Mediterranean diet”, “ketogenic diet”, and “neurodegenerative diseases and polyphenols” to locate pertinent studies. References from the retrieved articles were manually reviewed to ensure the inclusion of relevant literature. This review encompasses articles published in English up to August 8, 2025.

## 3. ALZHEIMER’S DISEASE AND DIET

According to the latest action plan on dementia by the World Health Organization (WHO), over 55 million people worldwide live with dementia. This number is expected to increase up to 78 million by 2030 and 139 million by 2050. Considering that there are approximately 9.9 million new cases of dementia globally each year, this image translates into new cases every three seconds [24]. The majority of individuals with dementia (60%) are seen in low- and middle-income countries, and most of the new cases are expected to be in those countries where the cases are increasing rapidly in the Far East and Sub-Saharan African regions due to extended life expectancy [25,26]. This disease is associated with impairments in multiple cognitive domains, particularly affecting short-term memory, judgment, and expressive speech [10–12,27]. AD is the most common cause of dementia [28]. Despite these findings, the pathogenesis of AD remains unclear [12]. Apart from the unexplained mechanistic details of Alzheimer's disease, three important hypotheses have been emphasized. These pathological hypotheses are the cholinergic, Aβ cascade and tau protein cascade hypotheses [29–31]. The first involves the accumulation of extracellular senile plaques composed of Aβ peptides. These peptides are generated through the sequential proteolytic cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase enzymes. The aggregation of Aβ in brain regions such as the hippocampus and cortex contributes to synaptic dysfunction and neuronal toxicity [32,33]. The second hypothesis focuses on the formation of intracellular neurofibrillary tangles (NFTs), which consist of

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hyperphosphorylated tau proteins. The accumulation of tau within neurons disrupts microtubule stability, impairs axonal transport, and ultimately leads to neuronal degeneration and synaptic loss [34]. Together, these pathological events play a central role in the progressive cognitive decline observed in AD [35]. In addition, mitochondrial autophagy is thought to be associated with various causes, such as the loss of synaptic and neurotropic factors [36]. The pathogenesis of AD is summarized in Fig. 1.

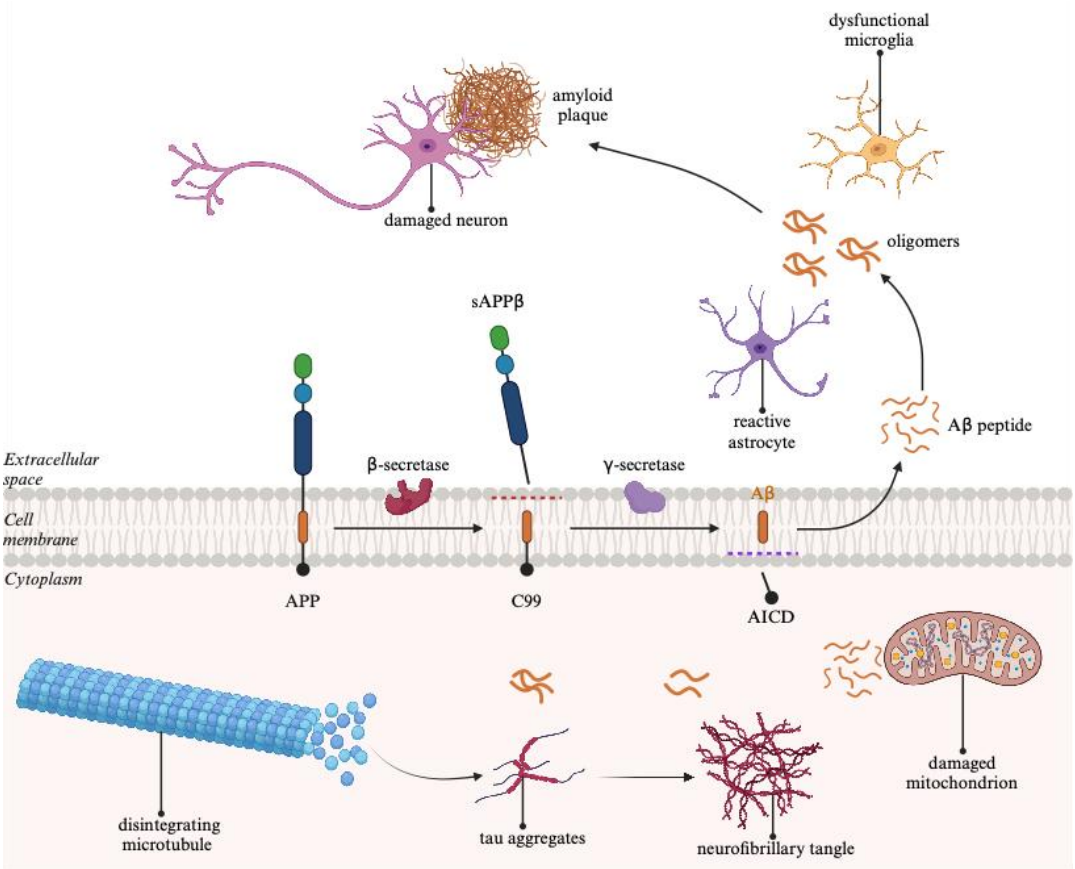


***Figure 1. The pathogenesis of AD***

OS is characterized by a disruption in the oxidants - antioxidants balance, leading to elevated levels of oxidants [37]. It is recognized as a significant clinical indicator of AD; however, it remains unclear whether OS is a causative factor or a consequence of the pathophysiological processes in the brains of AD patients. ROS and Aβ are primary contributors to OS. Resende et al. (2008) and Hartl et al. (2012) reported early onset of OS occurred prior to the accumulation of Aβ in mice model of AD. Within an oxidative environment, the production of Aβ may be influenced by the PS1 / γ-secretase complex. Notably, studies have shown that compounds such as 4-hydroxynonenal and 4,4-dithiodipyridine can induce a pathogenic rearrangement of PS1 subdomains within the γ-secretase complex, leading to increased aggregation and production of Aβ species [40]. Wang et al. (2021) further elucidated the complex interplay between ROS and Aβ, demonstrating that ROS can influence Aβ secretion and production, while Aβ itself can promote the excessive generation of ROS. Leuner et al. (2012) suggest that this cyclical interaction is evident in conditions where overproduction of Aβ, due to overexpression of APP, leads to decreased ATP production

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and respiratory control ratio, subsequently increasing ROS generation that indicates a self-perpetuating feedback loop between ROS and Aβ.

Antioxidants are substances capable of mitigating the detrimental effects of OS by significantly reducing the rate of oxidative reactions, even at low concentrations [43]. These compounds are typically categorized into two groups based on their action mechanisms; primary antioxidants, which neutralize free radicals and prevent the continuation of oxidative chain reactions, and secondary antioxidants, which oxidize to transform hydroperoxides into non-reactive products and enhance the effects of primary antioxidants. Secondary antioxidants are the main contributors to the regeneration of primary antioxidants, inactivation of metal ions, and the reduction of singlet oxygen levels. Given the crucial role of OS in AD, antioxidants have been proven beneficial in managing this condition [44]. The human body possesses a complex natural antioxidant defense system that protects against damage inflicted by pro-oxidants [45]. Research indicates that a variety of dietary sources can serve as antioxidants [46], categorizing the antioxidant system into two types: (1) the endogenous system, which the body naturally produces, and (2) the exogenous system, which is acquired through dietary intake.

Currently, AD is not curable, and current treatments have limited effectiveness [47]. Thus, increasing attention has recently paid to effective preventive options has been demonstrated recently [47,48]. Previous studies have suggested a possible effect of several diet models for the prevention of the dementia, especially AD, but the Mediterranean Diet (MeDi) model is probably the most focused on [49,50].

MeDi emerged in the 1960s as the dietary pattern of society living in Greece, Italy, and Crete [51]. When the nutritional patterns of societies living in these regions were examined, it was observed that there was diversity in food in their eating habits [52]. MeDi is based on whole grains, legumes, olive oil, seed oils, vegetables and fruits. In the traditional MeDi, consumption of kreatic foods such as milk and red meat, is limited [53].

The majority of studies on AD and MeDi have shown a beneficial effect of MeDi improving cognitive impairment in the overall population and in AD incidence, and a decreased mortality rate. Some cohort studies on the positive association of adherence to the MeDi on AD, patient numbers and patient origins can be summarized as: Anastasiou et al. (2017) among 1,865 elderly individuals in Greece, Qin et al. (2015) among over 65 years old 1,650 individuals in China, Féart et al. (2009) among 1,410 over 65 years old individuals in France, Zbeida et al. (2014) among 2,791 elderly individuals in the United States and 1,786 in Israel, Ye et al., (2013) among 1,269 Puerto Rican adults living in the United States, Tsivgoulis et al. (2013) among healthy 17,478 elderly individuals in the United States, Tangney et al. (2011) among 3,790 over 65 years old individuals in the United States, Gu et al. (2015) among 674 elderly individuals in the United States, Scarmeas et al. (2009) among 2,364 individuals in the United States, Wengreen et al. (2013) among 3,831 over 65 years old individuals in the United States have suggested the adherence to the MeDi has decreased the odds for dementia and cognitive impairment. Some double-blind randomized trial studies such as Valls-Pedret et al. (2015), have studied 447 healthy adults in Spain, and Martínez-Lapiscina et al. (2013), among 522 adults with high vascular risk in Spain have proven that the groups following the MeDi pattern had better cognitive function and lower mortality. Moreover, some observational studies such as Berti et al. (2018) among 70 healthy middle-aged individuals in the United States and Mosconi et al. (2014) among 52 healthy individuals in the United States, have also determined that MeDi was effective in preventing AD due to brain scanning and linked brain biomarker changes. On the other hand, some studies including Samieri et al. (2013), Cherbuin & Anstey (2012) and Vercambre et al. (2012) did not find any correlation between AD and cognitive impairment.

Adherence to MeDi can be translated into the combined consumption of various macronutrients and micronutrients including polyphenols, which are considerable neuroprotective agents against AD [71]. Previous studies have suggested that dietary polyphenols exhibit neuroprotective properties, including a range of effects on cerebral function, such as protecting neurons from injury and facilitating enhancements in memory, learning, and overall cognitive performance [72]. Thus, dietary polyphenols may represent an essential class of biomolecules for the formulation of therapeutic agents for AD.

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Catechins, the bioactive compounds predominantly found in green tea, include several varieties, including (−)-epigallocatechin gallate (EGCG), (−)-epicatechin (EC), (−)-epicatechin gallate (ECG), and (−)-epigallocatechin (EGC) which are known for their antioxidative properties, that involve scavenging ROS and metal ion chelating features [73,74]. Choi et al. (2001) reported that EGCG, in particular, decreased caspase levels and OS and reduced lipid peroxidation in the hippocampus in a rat model of AD. Haque et al. (2008) conducted a long-term study demonstrating that administion 0.5% green tea catechins helped mitigate Aβ-induced cognitive impairments and diminished ROS and plasma lipid peroxide in a rat model. In addition to their antioxidant effects, catechins have shown anti-inflammatory properties and the ability to inhibit AChE activity. Notably, EGCG has been shown to directly interact with amyloid-beta peptides, inhibiting their fibrillization and redirecting toxic oligomers into non-toxic forms [77,78]. Additionally, EGCG has demonstrated the ability to cross the blood-brain barrier in rodent models, further supporting its therapeutic relevance in neurodegenerative diseases [79,80].

Curcumin exhibits several properties that make it a promising neuroprotective agent, owing to its antioxidant, anti-inflammatory and anti-protein aggregate features [81]. Curcumin shows to mitigate neuroinflammation, oxidative stress, and cognitive deficits in AD models due to its antioxidant properties and inhibition of inflammatory signalling pathways[82] . Additionally, curcumin is known to bind metal ions, preventing the aggregation of Aβ and thereby reducing OS [83]. Furthermore, Nishinaka et al. (2007) and Lim et al. (2001) reported that curcumin could restore glutathione levels in brain tissues and decrease the levels of oxidized proteins in mouse models of AD. Similarly, resveratrol has been shown to enhance the levels of intracellular antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase and catalase, while also diminishing lipid peroxidation Kong et al. (2019). Previous studies have shown in both cell-line models and animal models that resveratrol possesses anti-amyloidogenic properties, effectively reducing the levels of secreted intracellular Aβ peptides S. K. Singh et al. (2018) as well as decreasing tau protein phosphorylation [87]. A crucial aspect of resveratrol function is its ability to decrease ROS production in brain tissue by maintaining mitochondrial membrane potential integrity [87]. The interaction of metal ions between Aβ and NFTs, promotes their accumulation and elevates ROS generation, which resveratrol mitigates by altering metal ion balance [88].

Moreover, alkaloids including tetrandrine and cryptolepine are anti-inflammatory compounds that suppress NF-κB [89]. J. A. Wang et al. (2020), Qiang et al. (2018) and Abulfadl et al. (2018) reported that terpenoids, including parthenolide, carnosol and artemisinin can inhibit the p38 MAPK and NF-κB signaling pathways in a mouse model of AD. Fang et al. (2012) demonstrated that ginsenoside Rg1, derived from the roots of ginseng plants significantly reduces Aβ levels in mose models of AD. Various natural plant extracts such as chrysophanol, crocin, aloe-emodin, and α-cyperone, have been identified for their roles in inhibiting tau protein formation and decelerating AD progression [94–96]. Caffeine, one of the most consumed alkaloids, has been reported to prevent Aβ aggregation in-vitro [97] and decrease ROS generation while enhancing SOD levels in Aβ-induced mouse model [98]. Furthermore, caffeine has demonstrated anti-neuroinflammatory effects and the ability to decrease tau protein phosphorylation in the hippocampus [99]. Moreover, caffeine inhibits AChE at low to moderate doses, thus enhancing cognitive function and slowing AD progression [100]. Despite these findings, the comprehensive impact of dietary patterns on AD remains underexplored in cross-sectional studies, highlighting the need for further research in this domain. Additionally, there is a general lack of awareness regarding the optimal quantities and qualities of bioactive components in foods that are necessary for significant neuroprotection [101].

## 4. HUNTINGTON'S DISEASE AND DIET

Huntington's disease (HD) is a neurodegenerative disease with autosomal dominant genetic inheritance and characterized by choreic (shaking, jumping) movement, psychological and behavioral disorders. Currently, HD is a deadly and ruthless disease, with an average life expectancy of 15-20 years following the onset of symptoms [102]. Although the number of cases is relatively low in Asia, it is seen in an average of 5.7 people

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per 100,000 people in Europe and America, and it is divided into two subgroups based on the age of onset [103]. However, recent studies have shown that the prevalence of the disease in Caucasians is 12 cases per 100,000 [104]. The age of disease onset can vary between 20-65 years. HD can generally be defined as a combination of motor, cognitive, and psychiatric disorders. Complex movement disorders called choreic movement, cognitive problems that affect managerial abilities, and psychiatric problems that often present with symptoms of apathy, depression and irritability are examples of these disorders [105].

The genetic basis of HD is neurological damage caused by the mutant huntingtin (mHTT) protein, which is formed by the excessive repetition of the glutamine-encoding CAG codon in the first exon of the HD gene on chromosome 4. Therefore, HD is a good example of a Mendelian genetic disease caused by a single identified mutation linked to a single gene [106]. If the CAG number of repetitions exceeds thirty-five, a pathological condition occurs with high probability [107]. Studies have shown that CAG repeats in the gene increase with age, and that the length of CAG repeats affects the progression and severity of the disease [108–110].

The toxic effects of mHTT are diverse, and many pathways are disrupted in its presence [111]. Although several therapeutic options exist for treating symptoms and signs, no approach designed to target these pathways has slowed or stopped the progression of HD in humans [102]. OS plays a critical role in the pathogenesis of HD, indicating potentially overlapping pathological pathways triggered by distinct causative factors. In HD, the toxicity mechanism specific to this condition involves mitochondrial dysfunction, which is mediated by a mutant HTT protein [112,113]. Fig. 2 shows some selected mechanisms that play a role in HD pathogenesis.

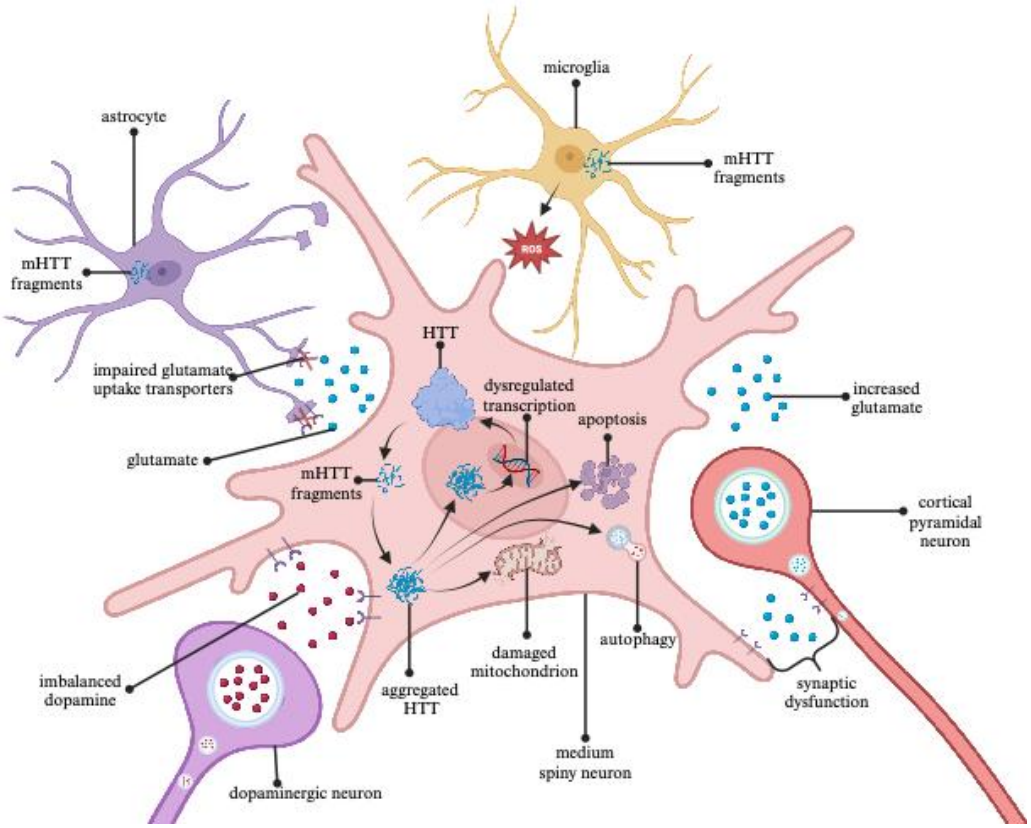


***Figure 2. The pathogenesis of HD***

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Studies have highlighted diminished activities in the respiratory chain complexes and enzymes of the tricarboxylic acid cycle in the brain tissues of HD patients. Such mitochondrial dysfunction leads to a cascade of detrimental effects including reduced mitochondrial biogenesis, increased OS, depleted ATP levels, and heightened apoptosis within the HD context. It has been established that aconitase activity is highly sensitive to modulation by ROS, reactive nitrogen species, hydroxyl radicals, and other harmful molecules [114,115]. Previous studies have shown that diet and caloric intake can affect phenoconversion and disease severity in HD [116]. The association between HD and some dietary models, micro and macronutrient intake, food supplementation, and polyphenol consumption found in the literature will be discussed below.

The roles of the MeDi and dietary intake in providing neuroprotection and delaying disease progression in HD are not well-understood. However, some selected studies on the positive correlation of adherence to the MeDi and phenoconversion and course of the disease, patient numbers and origins can be summarized as follows: Rivadeneyra et al. (2016) among 98 participants aged 38-60 in Spain, Rivadeneyra-Posadas et al. (2022) among 42 participants aged between 40-64 in Spain, Cubo et al. (2015) among 224 participants aged between 33-61 years in Spain, Christodoulou et al. (2023) among 73 participants aged between 18-75 in Cyprus, and Marder et al. (2013) among 211 participants aged between 25-57 in the United States and Canada. All the mentioned studies emphasized that patients with HD showed low MeDi adherence, and higher MeDi adherence was associated with higher quality of life and better nutritional composition.

Considerable evidence suggests that mitochondrial dysfunction in the brain and skeletal muscles plays a key role in HD pathogenesis. Metabolic interventions, such as fasting and ketogenic diets (KeDi), are theorized to potentially boost metabolism and mitochondrial functionality in the brain and muscles, which could ameliorate the clinical symptoms of HD. Phillips et al. (2022) conducted a case study of a 41-year-old male with advanced HD who followed time-restricted KeDi for 48 weeks. The patient experienced a 52% improvement in motor symptoms, 28% enhancement in activities of daily living, a 20% increase in the composite Unified Huntington's Disease Rating Scale (UHDRS) score, and a 50–100% improvement in behavioral problems related to HD, including apathy, disorientation, anger, and irritability. Additionally, his mood-related quality of life had improved by 25%. Whittaker et al. (2022) investigated the ameliorative effect of KeDi in an HD mouse model, and the intervention was observed to improve activity rhythms, enhance rhythmic power, decrease inappropriate daytime activity and variability in onset times, and enhance motor performance in the rotarod and challenging beam tests.

While adherence to MeDi and KeDi plays an important role in the course of HD, studies have indicated varying effects of different dietary components on the age of HD onset. Buruma et al. (1987) observed a significant relationship between the consumption of dairy, particularly milk, which was found to correlate negatively with the age of onset, suggesting that higher dairy consumption could lead to an earlier onset of the disease. Simonin et al. (2013) reported the effect of caffeine consumption on the age of onset and progression of motor and functional decline in HD. It was found that higher average caffeine intake, particularly > 190 mg/day before the onset of the disease, was linked with an earlier age at onset. Marder et al. (2009) examined macronutrient consumption in relation to HD, and showed that carbohydrate consumption was notably higher in the group with CAG ≥ 37. Additionally, caloric intake was significantly associated with CAG repeat length and estimated 5-year probability of HD onset in individuals with expanded CAG repeats.

HD has shown promising responses to flavonoids in scavenging free radicals and reducing OS. This has been evidenced by various cell and animal studies [127,128]. However, clinical trials specifically testing flavonoids and antioxidants for HD are limited and have yielded mixed outcomes.

Mähler et al. (2013) investigated the effects of EGCG in HD patients using a multicenter, randomized, double-blind, placebo-controlled trial. Among 54 individuals with HD, the trial administered 1200 mg/day of EGCG for 12 months. Cognitive improvements were assessed using the UHDRS and included tests such as the Stroop Test, Verbal Fluency Test, and Symbol Digit Modalities Test. These findings indicate that EGCG leads to cognitive enhancements in HD patients.

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In contrast, other antioxidants such as d-tocopherol have demonstrated efficacy in decelerating motor decline in early-stage HD patients [130], whereas synthetic antioxidants such as idebenone and OPC-14117 did not show significant improvements in cognition or free radical scavenging in clinical trials involving 100 and 64 HD patients, respectively [131,132].
While flavonoids such as quercetin [133], naringin [134], hesperidin [135] and rutin [136] have demonstrated potential in preventing and alleviating symptoms in animal models of HD, and there remains a significant gap in clinical research. These compounds should be evaluated in human trials, ideally in combination with other promising treatments, to establish their therapeutic viability.

## 5. HUNTINGTON'S DISEASE AND DIET

Parkinson's disease (PD), the second most common neurodegenerative disorder after AD, affects about 1% of those over 60 in Europe and North America [137]. Symptoms of PD commonly include muscle rigidity, slowed movement, postural instability, and resting tremors, primarily due to the targeted degeneration of dopaminergic neurons in the substantia nigra pars compacta. Neuron loss is a key pathological feature of PD. Additionally, non-motor symptoms such as depression, REM sleep behavior disorders, autonomic dysfunction, olfactory deficits, and constipation, are also prevalent and often appear as early prodromal signs of the disease [138].
PD largely occurs sporadically, yet 5–10% of cases are hereditary, often linked to the protein alpha-synuclein (α-syn). α-syn was the first protein associated with genetic forms of PD and is a major component of Lewy bodies and Lewy neurites, which is another hallmark of PD pathology [139,140]. PD is a multifactorial disease, in which both genetic predispositions and environmental factors contribute to its onset [141,142]. The etiology of PD involves OS, supported by evidence showing the brain's vulnerability due to its high metabolic demand and oxygen consumption. Notably, the antioxidant glutathione level is lower in the substantia nigra than in other brain regions [143]. The presence of dopamine in dopaminergic neurons also increases susceptibility to oxidative damage, as evidenced by the elevated oxidative modifications observed in DNA, lipids, and proteins in post-mortem PD brain analyses [144].
Pathological characteristics, including mitochondrial dysfunction and neuroinflammation, are known to enhance oxidative damage in PD. Dysfunctional mitochondria, a primary source of intracellular ROS production, exacerbate this damage when the electron transport chain is impaired [145]. Chronic neuroinflammatory responses also contribute to enzymes, such as NADPH oxidase and inducible NO synthase, which promote the formation of harmful radicals [146]. These factors, along with evidence of impaired mitochondrial complex I activity and the existence of reactive microglia in post-mortem studies, underline the role of mitochondrial dysfunction and neuroinflammation in the pathology [147].
Moreover, proteins associated with PD, such as α-syn, parkin, PINK1, DJ-1, and LRRK2, are linked to mitochondrial function or influence microglia activation, further supporting the association between mitochondrial impairment, neuroinflammation, and ROS production in PD [145]. Alteration of redox homeostasis in PD can lead to neuronal degeneration by disrupting protein homeostasis (proteostasis), which is crucial for long-lived, post-mitotic cells such as neurons. OS impairs proteostasis by contributing to protein misfolding, thereby mimicking the effects of genetic mutations linked to PD. This affects both the ubiquitin-proteasomal and autophagy-lysosomal systems [148,149]. PD pathology is characterized by the accumulation of misfolded α-syn oligomers and fibrils, and the prion-like spread of α-syn aggregates through mechanisms such as tunneling nanotubes, exosomes, and secretion plays a critical role in disease progression [150]. The pathogenesis of PD is shown in Fig. 3.

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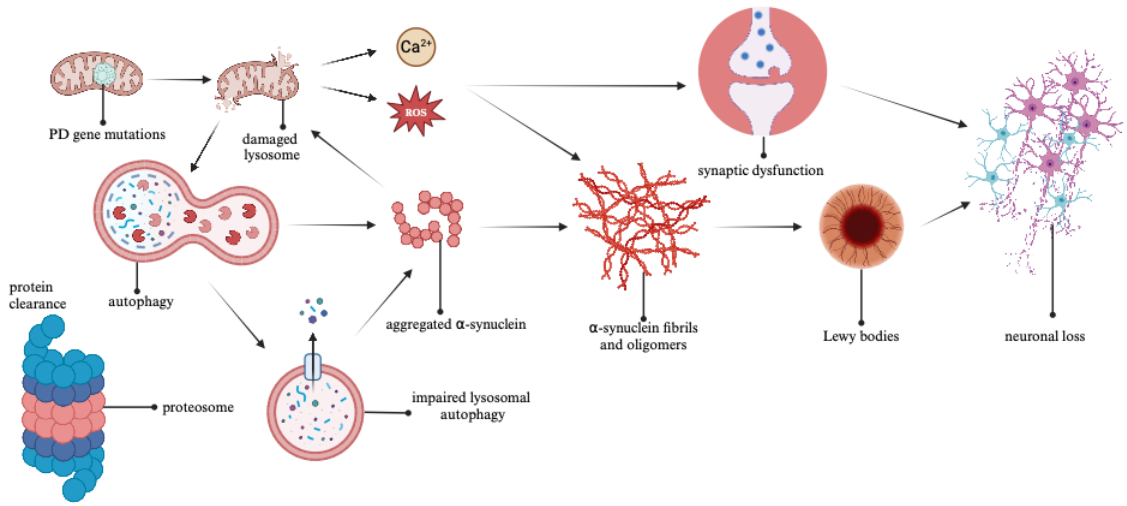


***Figure 3. The pathogenesis of PD***

Although the influence of environmental factors on the development of PD is well recognized [151], studies examining the relationship between PD risk and specific dietary components have yielded mixed results [152,153].

As discussed above, OS has been identified as a key element in PD development [154,155]. MeDi has garnered significant interest due to accumulating evidence that suggests a lower risk of neurodegenerative and cardiovascular diseases, various cancers, and overall mortality associated with adherence to this diet [156]. Substances, such as complex phenols, vitamin C, vitamin E, and carotenoids, which act as antioxidants, are abundant in the typical components of MeDi and may contribute to its beneficial effects. Adherence to MeDi may reduce inflammation and thus lower the risk [157]. Additionally, the MeDi's protective potential may be due to its lower content of compounds, such as animal fats, which are linked with increased PD risk. Previous studies have established an association between high consumption of animal fats [50] and increased PD risk as well as a known link between higher dairy intake and greater PD risk [158,159]. A study conducted by Alcalay et al. (2012) among 257 participants with PD and 198 participants without PD in the United States showed that lower adherence to MeDi was linked to early PD age at onset. Similar results were found in a population-based cohort study among 47,000 Swedish women, which showed that MeDi adherence was related to a lower PD risk [161]. Paknahad et al. (2020) suggested MeDi adherence increased the executive function, attention, concentration, language, and active memory, as well as the total cognitive evaluation score of participants with PD in Iran.

As OS and neuroinflammation are established contributors to PD and the protective effects of MeDi may stem from its antioxidant properties, key components of polyphenols, vitamins, and polyunsaturated fatty acids, especially omega-3 (ω3-PUFAs), have been extensively studied for their protective capabilities [163]. Fruits, vegetables, and herbs, which are rich in vitamins and polyphenols, provide antioxidant benefits that may help counteract redox imbalances, potentially reducing the risk of developing PD [164]. A comprehensive prospective study spanning two decades and involving nearly 130,000 participants in the United States revealed that men who frequently consumed foods and beverages rich in flavonoid had a lower risk of developing PD up to 40%. This association was particularly strong with a high intake of anthocyanins, berries rich in anthocyanins, and apples, which was correlated with a lower PD risk.

Guo et al. (2007) reported that a seven-day pretreatment with green tea polyphenols, including EGCG, EC, ECG, and EGC at doses of 150 and 450 mg/kg/day, administered orally, protected dopaminergic neurons in the striatum and midbrain from 6-OHDA-induced cell death in a rat model of PD. This protective effect is

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associated with a reduction in nitric oxide synthase (NOS) levels, decreased levels of ROS and nitric oxide (NO), reduced lipid peroxidation, and enhanced free radical scavenging activity in the nigrostriatal region. Similarly, studies conducted by Tan et al. (2003), L. C. Tan et al. (2008), Kandinov et al. (2009), Mak (2012) and F. J. Li et al. (2012) confirmed the long-term benefits of tea consumption on PD risk and onset motor symptoms. Bakoyiannis et al. (2019) and Haleagrahara et al. (2011) investigated the anti-PD properties of quercetin, the major flavonoid present in leaves and fruits, and reported that quercetin administration reduced OS in the striatum and dopaminergic neuronal loss at the PD rat model, as evidenced by the increased levels of antioxidant enzymes such as glutathione. Z. H. Wang et al. (2015) reported that resveratrol treatment in a mouse model of PD decreased the expression of α-syn, which is the pathological hallmark of PD, and increased the expression of miR-21. Research has suggested that the ability of resveratrol to regulate α-syn is associated with the AMPK-SIRT1-authopthagy pathway.

As seen above, dietary adjustments may affect both motor and non-motor symptoms of PD; however, there is debate over the optimal fat-to-carbohydrate ratio [174]. On the one hand, a diet low in fat and high in carbohydrates could facilitate the transport of the dopamine precursor, tyrosine, into the cerebrospinal fluid and might prompt an insulin-induced increase in brain dopamine levels [175,176]. Additionally, increasing dietary fiber intake could theoretically improve the fermentation of neuroactive short-chain fatty acids in the gut, potentially influencing gut motility in PD [177,178]. Conversely, impairments in respiratory chain complex I activity observed in the frontal cortex and substantia nigra of patients with PD could potentially be bypassed by the ketones generated from a high-fat, low-carbohydrate KeDi [179]. This diet may support mitochondrial oxidative phosphorylation in the brain through a complex II-dependent pathway and promote energy metabolism in central and peripheral neurons by stimulating mitochondrial biogenesis [180]. [181] investigated the effects of a low-carbohydrate/healthy fat KeDi on depression, anxiety, and biomarkers in 16 participants with PD. It was determined that 12 weeks of KeDi intervention improved the Parkinson's Anxiety Scale (PAS), United Parkinson's Disease Rating Scale (UPDRS) scores, and biomarkers of participants. In a case study conducted in the United States, a 68 years old female with PD followed the traditional KeDi protocol for 24 weeks. KeDi adherence improved all health biomarkers, reduced HbA1C, C-reactive protein, triglycerides, and fasting insulin levels, as well as weight loss in the patient [182]. Intriguing findings were presented by Phillips et al. (2018), who compared the effects of a low-fat diet versus KeDi in 47 PD patients for 8 weeks. Both dietary patterns received the same number of calories daily. While noteworthy improvements in both motor and non-motor symptoms were observed in both groups, KeDi participants exhibited greater improvements in non-motor symptoms.

## 6. AMYOTROPHIC LATERAL SCLEROSIS AND DIET

Amyotrophic lateral sclerosis (ALS) is an incurable motor neuron disorder, with a prevalence of approximately 1/2,000 individuals [184,185]. However, a larger number of ALS cases are sporadic (sALS), with only about 10% being familial (fALS) [186]. ALS is characterized by progressive loss of upper and lower motor neurons in the brain and spinal cord, eventually leading to paralysis of voluntary muscles. This degeneration results in escalating motor dysfunction that affects the respiratory system and typically leads to patient death within 2-5 years [187].

The pathogenesis of ALS is generally understood to involve oxidative control loss, resulting in excessive ROS production, neurofilament accumulation, and excitotoxicity due to increased glutamate levels, which leads to mitochondrial membrane dysfunction [188]. This dysfunction disrupts energy balance by decreasing the activity of mitochondrial electron transport chain (ETC) enzymes in the spinal cord [189].

Specifically, in 20% of sporadic cases involving mutant SOD1 forms, there is a great deprivation of mitochondrial membrane potential and mitochondrial inflammation, which reduces ATP production, disrupts calcium homeostasis, and decreases mitochondrial transport chain enzyme activity, ultimately leading to the mentioned bioenergetic alterations [190].

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OS, significantly contributes to neuronal death, either directly or as a consequence of other pathogenic mechanisms [191], primarily through ROS. OS plays a critical role In fALS, as evidenced by elevated levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of motor cortex oxidation in ALS patients [192].
The susceptibility of ALS to high levels of OS is exacerbated by the excessive reactivity of ROS with DNA, proteins, and lipids, inducing significant cellular damage [193]. The nervous tissue's rich lipid content and high metabolic activity of neurons further increases ROS production [194].
Mitochondrial dysfunction is also closely associated with motor neuron disorder. Morphological changes in mitochondria have been observed in SOD1 mice and sALS patients without SOD1 mutations [195]. These changes include ETC alterations and mitochondrial DNA mutations, which contribute to disease pathogenesis [196]. The resulting mitochondrial damage increases intracellular Ca++ and disrupts ETC functioning, leading to further ROS production and a cascade of oxidative damage through caspase activation [196]. Fig. 4 illustrates the pathogenesis of ALS.

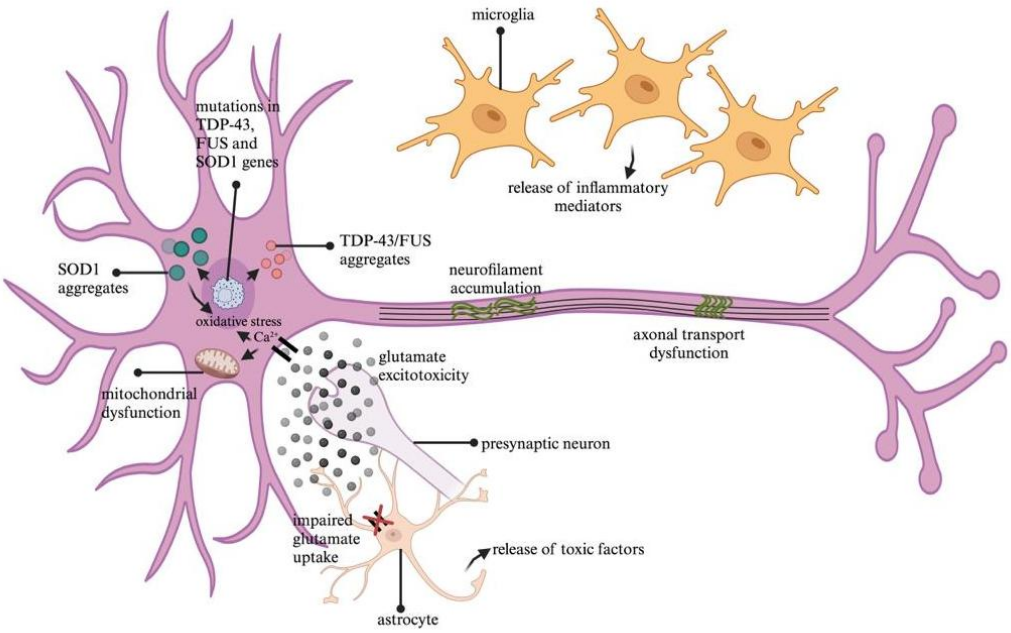


***Figure 4. The pathogenesis of ALS***

Considering the altered energy balance in ALS, increasing carbohydrate intake appears less favorable due to metabolic alterations in cerebral glucose processing in ALS patients [197]. This is further verified by 1H-NMR based metabolomic profiling of CSF, indicating altered metabolite levels, including ketone bodies like acetate and acetone [198]. ALS patients also face an escalated risk of diabetes mellitus, possibly due to SOD1 gene defects affecting glucose metabolism [199,200]. Early studies have shown a repression of glycolytic capacity in muscle fibers of mice induced with SOD1, suggesting a shift away from carbohydrate reliance for energy [201]. Therefore, increasing dietary fat, particularly sources like butter and coconut oil rich in ketone bodies, may offer a more effective energy alternative, reducing disease risk and slowing progression [202].

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These findings suggest that enhancing mitochondrial function could be a viable therapeutic strategy for ALS [203]. Given the success of MeDi and KeDi in managing other neurodegenerative diseases, dietary interventions could improve mitochondrial function in ALS patients.

MeDi, as discussed in other sections, is widely recognized as one of the richest in antioxidants and also has been suggested to alleviate ALS symptoms, largely due to its ability to reduce the OS associated with neuronal death in ALS. De Paola et al. (2016) reported that an extract from extra virgin olive oil appears to be a neuroprotective agent in the SOD1 mouse model by reducing NO production from glia activated by the SOD1 mutation. This study also indicated that the toll-like receptor 4 (TLR4) signaling pathway, implicated in ALS pathology, was down-regulated by the use of olive oil extract. The hydroxytyrosol (HT) content in olive oil, known for its anticancer, anti-inflammatory, and antioxidant properties, further underscores its potential benefits [205]. Moreover, Oliván et al. (2014) found that supplementing diets with olive oil, emulating a traditional MeDi, improved pathological consequences and delayed disease onset in ALS mouse models compared with control mouse chow. These findings support the potential for early intervention using MeDi in ALS owing to its antioxidant and neuroprotective capabilities. Furthermore, some of the main antioxidative components of MeDi against ALS have been comprehensively investigated. In the literature, carotenes [207], fisetin [208], quercetin [209], resveratrol [210,211] and EGCG [212,213] have been reported to be associated with a delay in the onset of the disease through various mechanisms such as reduced OS, modulation of metabolic pathways and interaction with mutant SOD1.

Interestingly, a clinical pilot study in 2023 by Carrera-Juliá et al. on Spanish participants explored the effects of a MeDi fortified with antioxidants pterostilbene (PTER) and nicotinamide riboside (NR) and a version combined with coconut oil, akin to KeDi. This study reported significant improvements in anthropometric measures among participants on these diets compared with those in the control group. NR and PTER are known to reduce OS, whereas coconut oil has been identified as a potential mediator of mitochondrial dysfunction [215,216].

Research on the potential benefits of ketogenic bodies (KBs) in ALS in animal models has indicated promising results. [217] reported that KeDi supplemented with caprylic triglycerides from fractionated coconut oil preserved motor neurons and enhanced motor performance in a mouse model of ASL compared to controls on an isocaloric diet. KeDi also improved mitochondrial ATP synthesis and weight maintenance. In another study, W. Zhao et al. (2012) suggested that these improvements were linked to elevated mitochondrial oxygen consumption and increased blood KB levels, with a longer animal survival duration. Endogenous antioxidants such as glutathione peroxidase, catalase, and SOD help counteract ROS and mitigate oxidative damage. KBs have been shown to enhance the antioxidant capacity of these enzymes [219,220]. Moreover, KBs can regulate glutamate levels in the synaptic cleft, reducing hyperexcitability and inflammation, and potentially improving ALS progression [221].

The impact of fat consumption on ALS remains controversial, as evidenced by conflicting findings in the literature [222]. Nelson et al. (2000) found that a higher intake of fat was associated with an increased risk of developing ALS, while Okamoto et al. (2007) suggested that a greater consumption of fat was associated with a decreased risk of ALS onset [223,224].

***Table 1. indicates a summary of studies on the association of adherence to MeDi and neurodegenerative diseases mentioned in this review.***

| Dis. | Subject | Country | Method | Findings | Ref. |
|---|---|---|---|---|---|
| AD | 1,865 individuals, mean age 73±6, 90 with dementia, 223 with mild cognitive impairment | Greece | Food frequency questionnaire | Adherence to MeDi was associated with a 10% decrease in the odds for dementia, with better performance in memory, language, visuospatial perception and the composite cognitive score; the associations were strongest for memory. Fish consumption was negatively associated with dementia and cognitive performance positively associated with non-refined cereal consumption. | [54] |

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| | | | | | |
|---|---|---|---|---|---|
| AD | 1,650 individuals ≥55 years of age | China | China Health and Nutrition Survey | Among adults ≥65 years of age, adherence to MeDi was associated with slower rate of cognitive decline, no association was observed among participants <65 years of age. | [55] |
| AD | 1,410 adults ≥65 years of age | France | Food frequency questionnaire | Higher Mediterranean diet score was associated with fewer Mini-Mental State Examination errors and better Cued Selective Reminding Test results. | [56] |
| AD | 2,791 individuals with mean age 71.2 and 1786 individuals with mean age 74.9 | USA and Israel | US National Health and Nutrition Survey and Israeli National Health and Nutrition Survey | Adherence to MeDi was associated with higher scores in cognitive function questionnaire and Physical Function Questionnaire. | [57] |
| AD | 1,269 Puerto Rica heritage individuals, aged 45-75 | USA | Food frequency questionnaire | Greater adherence to the MeDi was associated with higher Mini Mental State Examination score, lower likelihood of cognitive impairment. | [58] |
| AD | 17,478 adults ≥45 years of age | USA | Food frequency questionnaire | Higher adherence to MeDi was associated with lower likelihood of incident cognitive impairment. | [59] |
| AD | 3,790 adults aged ≥65 | USA | Chicago Health and Aging Project | Higher MedDi scores were associated with slower rates of cognitive decline | [60] |
| AD | 674 elderly individuals with mean age 80.1 | USA | Food frequency questionnaire | MeDi adherence was associated with less brain atrophy, with an effect similar to 5 years of aging. | [225] |
| AD | 2,364 participants, 564 with mild cognitive impairment | USA | Food frequency questionnaire | Higher adherence to the MeDi is associated with a trend for reduced risk of developing mild cognitive impairment and with reduced risk of mild cognitive impairment conversion to AD. | [62] |
| AD | 3,831 participants aged ≥65 | USA | Food frequency questionnaire | Higher levels of accordance with MeDi were associated with consistently higher levels of cognitive function in participants over an 11-y period. Whole grains and nuts and legumes were positively associated with higher cognitive functions. | [63] |
| AD | 447 cognitively healthy participants with mean age 66.9 | Spain | Dieta Mediterránea nutrition intervention trial | In an older population, MeDi supplemented with olive oil or nuts was associated with improved composite measures of cognitive function. | [64] |
| AD | 522 participants at high vascular risk with mean age 74.6 ± 5.7 years | Spain | MeDi intervention suppmeneted with extra virgin olive oil and nuts | Participants allocated to the MeDi+Extra virgin olive oil showed higher mean Mini-Mental State Examination and Clock Drawing Test scores with significant differences versus control. | [65] |
| AD | 70 cognitively healthy participants aged 30-60 | USA | Harvard food frequency questionnaire | Lower MeDi adherence was associated with progressive AD biomarker abnormalities in middle-aged adults. | [66] |
| AD | 52 cognitively healthy participants, | USA | Harvard/Willett's semi-quantitative food | Cognitively healthy individuals showing lower adherence to the MeDi had cortical thinning in the same brain regions as clinical AD patients compared to those showing higher adherence. | [67] |

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| | | | | | |
|---|---|---|---|---|---|
| | mean age 54+12 | | frequency questionnaire | | |
| HD | 98 participants aged 30-60 with HD | Spain | Food frequency questionnaire | MeDi adherence is associated with better quality of life, lower comorbidity, lower motor impairment and lower risk for abdominal obesity. | [117] |
| HD | 42 participants aged 40-64 with HD | Spain | Food frequency questionnaire | MeDi adherence protects against low physical performance and severity sarcopenia in HD. | [118] |
| HD | 224 participants aged 33-61 with HD | Spain | Food frequency questionnaire | Adherence to MeDi prevents against weight loss in patients with advanced HD, but it is not associated with better functional state. | [119] |
| HD | 73 participants with HD aged 18-75 | Cyprus | Cyprus food frequency questionnaire | Adherence to MeDi was associated with the severity of HD symptoms. | [120] |
| HD | 211 participants with ≥37 CAG repeat length aged 26-57. | USA and Canada | Semiquantitative food frequency questionnaire | MeDi was not associated with phenoconversion; however, higher consumption of dairy products had a 2-fold increased risk. | [121] |
| PD | 257 with PD and 198 without PD participants | USA | The Willett semiquantitative food frequency questionnaire | Higher MeDi adherence was associated with reduced odds for PD, and lower adherence was associated with earlier PD age at onset. | [160] |
| PD | 47,000 female participants | Sweden | Food frequency questionnaire | Higher adherence to a MeDi at middle age was associated with lower risk for PD. | [161] |
| PD | 80 participants with idiopathic PD mean age 59 | Iran | MeDi intervention | The mean score of the dimensions of executive function, language, attention, concentration, and active memory and the total score of cognitive assessment significantly increased with the MeDi intervention. | [162] |
| ALS | 747 participants with ALS, 2385 control participants | Netherlands | Food frequency questionnaire | Higher adherence to MeDi was associated with decreased risk of ALS. | [226] |
| ALS | 10 participants with ALS | Spain | MeDi intervention | Adherence to MeDi was associated with body weight and waist circumference improvements in both male and female patients. | [227] |

## 7. CONCLUSIONS

Extensive in-vivo and in-vitro studies as well as the clinical trials presented in this review, show that dietary factors play an important role in the onset, progression, and potential mitigation of symptoms associated with neurodegenerative diseases. In particular, MeDi and KeDi have been identified as beneficial dietary patterns that can influence the course of these diseases. The high antioxidant content of MeDi, which includes a variety of fruits, vegetables, herbs, whole grains, and olive oil, has shown potential in improving cognitive status and reducing the risk of neurodegenerative diseases, especially AD and PD. Similarly, KeDi, which is rich in fats and low in carbohydrates, improves mitochondrial function and increases metabolic efficiency, potentially providing neuroprotective effects in diseases such as ALS and HD.
Furthermore, the roles of specific nutrients and dietary supplements in the management of neurodegenerative diseases have been explored. Especially dietary polyphenols were studied for their antioxidant and

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neuroprotective properties, which may counteract OS and inflammation implicated in these diseases. Compelling research also highlights that polyphenols can suppress the activation of neuroinflammatory pathways, triggered by abnormal protein accumulations, by inhibiting microglial activation. This results in the decreased production of inflammatory cytokines and supports neuronal health. Behavioral assessments align with these findings, noting significant improvements in motor functions—ranging from enhanced mobility to reduced involuntary movements, and better overall motor coordination.

However, results from clinical trials and epidemiological studies have been mixed, suggesting that while diet can play a crucial role in disease management, yet it is not a standalone solution. The complexity of neurodegenerative diseases calls for a multifaceted approach that considers genetic, environmental, and lifestyle factors. Future research should continue to explore the interaction between diet and disease mechanisms, aiming to refine dietary recommendations and develop targeted nutritional therapies that could complement the existing treatments. Moreover, as the global burden of these diseases increases, preventive dietary strategies could be key to reducing incidence rates, particularly in vulnerable populations.

In conclusion, while significant strides have been made to understand the impact of diet on neurodegenerative diseases, much remains to be explored. The potential of dietary interventions to alter disease progression, improve the quality of life, and possibly delay the onset of clinical symptoms is promising. Ongoing and future studies will be crucial for substantiating the role of diet in neurodegeneration and opening new avenues for effective interventions.

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