Research article

Effects of natural antioxidants in neurodegenerative disease

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Polyphenols are secondary metabolites with antioxidant properties and are abundant in the diet. Fruits, vegetables, herbs, and various drinks (tea, wine, and juices) are all sources of these molecules. Despite their abundance, investigations into the benefits of polyphenols in human health have only recently begun. Phenolic compounds have received increasing interest because of numerous epidemiological studies. These studies have suggested associations between the consumption of polyphenol-rich aliments and the prevention of chronic diseases, such as cancer, cardiovascular diseases, and neurodegenerative diseases.

More specifically, in the last 10 years literature on the neuroprotective effects of a polyphenol-rich diet has grown considerably. It has been demonstrated, in various cell culture and animal models, that these metabolites are able to protect neuronal cells by attenuating oxidative stress and damage. However, it remains unclear as to how these compounds reach the brain, what concentrations are necessary, and what biologically active forms are needed to exert beneficial effects. Therefore, further research is needed to identify the molecular pathways and intracellular targets responsible for polyphenol's neuroprotective effects. The aim of this paper is to present various well-known dietary polyphenols and their mechanisms of neuroprotection with an emphasis on Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

Keywords: Amyotrophic lateral sclerosis, Antioxidants, Alzheimer's disease, Brain aging, Neuroprotection, Parkinson's disease, Oxidative stress

Introduction

The theory of free radicals in the aging process was first formulated by Harman in the 1950s. Consequent studies have indicated that oxidative damage (OD) constitutes a mechanism of injury found in many types of age-related diseases.[1] As we age, antioxidant defenses become attenuated. This results in the increase of OD which is considered an important causative factor in age-related diseases such as Alzheimer's and Parkinson's.[2] Neurodegenerative diseases such as these are becoming increasingly prevalent; therefore, research on the aging brain as a risk factor in the development of these diseases is of paramount importance.

Natural antioxidant molecules have been proposed as an alternative form of treatment for the prevention of age-related neurological diseases. Different types of antioxidant molecules (polyphenols and carotenoids) and traditional antioxidant vitamins (vitamin C and E) may contribute to this prevention. Epidemiological studies have indicated significant differences in the incidence of various diseases among ethnic groups that have different alimentation practices. For example, epidemiological evidence has shown that the Mediterranean diet, which is rich in antioxidants, is effective in the prevention of age-related diseases such as Alzheimer's.[3–8] Many of the benefits derived from the consumption of these antioxidant-rich diets may be the result of a synergy between natural antioxidants such as polyphenols, isoprenoid compounds, and vitamins.[9] This review focuses on the molecular mechanisms responsible for the antioxidant capacity of polyphenols and their roles in the prevention of age-related neurological diseases.

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The brain and oxidative stress

The brain is particularly vulnerable to oxidative stress (OS). It requires very high amounts of oxygen per unit of weight ($\sim$20% in humans). It also has a high content of oxidizable polyunsaturated fatty acids, especially 20:4 and 22:6 fatty acids. These are highly susceptible to lipid peroxidation and the presence of redox-active metals (Cu and Fe).[2,10,11] Compounding the issue is the brain's relative deficiency in antioxidant systems.[2] Furthermore, energy metabolism of the brain depends exclusively on glucose utilization and its complete oxidation in the mitochondria via the Krebs cycle and electron transport chain (ETC).[12] The ETC is composed of complexes I (NADH ubiquinone oxidoreductase), II (succinate ubiquinone oxidoreductase), III (ubiquinone cytochrome c reductase), IV (cytochrome oxidase), and V (F_1F_0-ATP synthase).[13] The majority of reactive oxygen species (ROS) (95–98%) are produced by the ETC during aerobic metabolism.[14] It has been estimated that up to 2% of the O_2 consumed during aerobic metabolism is converted into the free radical superoxide. This percent increases in damaged and aged mitochondria. Mitochondrial complexes I and III are predominant sites of free radical production, and damaged complexes II and IV can also lead to the generation of ROS in pathological conditions.[15–17]

ROS are well-recognized for being both detrimental and beneficial to biological systems.[18–20] These molecular species are beneficial because they are an integral component of cellular signaling and are essential to normal growth and metabolism.[18] This explains why cells exhibit a low level of OS. These levels are required and are maintained by ROS scavenging mechanisms, such as catalase and manganese superoxide dismutase (Fig. 1).[19,20] OS incurs from a disturbance in the balance between free radical production and scavenging. This results in the accumulation of excess ROS which damages cellular lipids, proteins, and DNA, thereby, attenuating their normal function (Fig. 2). Therefore, under normal and pathological conditions, mitochondria are the primary source of ROS and primary target of OD.
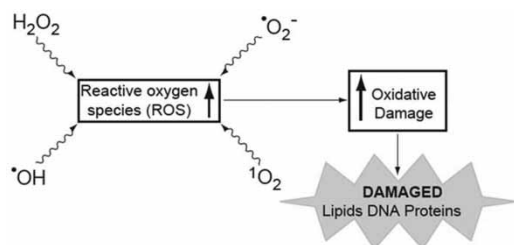

Figure 1 Reactive oxygen species produced during mitochondrial metabolism. The increased production of ROS in addition to the decreased antioxidant capacity within the cell results in damaged DNA, lipids, and proteins.
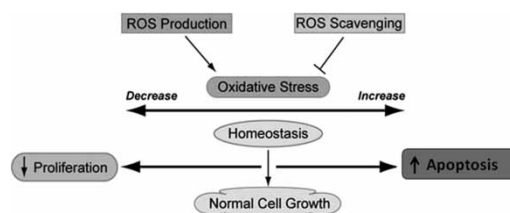

Figure 2 Redox homeostasis and its cellular impact. Maintenance of "redox homeostasis" is crucial for normal cell function. An imbalance can lead to apoptosis or decreased cell proliferation.

OS and damage in neurodegenerative disease

The OS theory of neurodegeneration proposes that an excess of free radicals leads to the death of nerve cells via the accumulation of mitochondrial OD. More specifically, damage of mitochondrial DNA and protein, caused by OD, results in two major detrimental effects. It increases the release of ROS within the mitochondria and attenuates ATP synthesis.[21] These defects in mitochondrial energy metabolism result in the decrease of high-energy phosphates, deterioration of membrane potential, and disruption of calcium homeostasis.[22]

Mitochondria have a high capacity to sequester Ca^{2+} which contributes to the functionality of neurons.[23–25] Mitochondrial calcium dysregulation along with high levels of ROS, mitochondrial DNA (mtDNA) mutations, and decreased mitochondrial respiration have been widely observed in many neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis (ALS).[26–31] Calcium homeostasis can be disrupted by the hyperactivation of N-methyl-D-aspartate (NMDA)-type receptors. In neurodegenerative diseases, this results in glutamate-induced excitotoxicity which can lead to neuronal death.[32] Hyper-activation of NMDA-type receptors increases the concentration of Ca^{2+} which can induce the mitochondrial transition pore (MTP) to open. This results in osmotic swelling and collapse of the outer mitochondrial membrane. The MTP is a multiprotein complex composed of a voltage-dependent anion channel, adenine nucleotide translocase, and regulatory protein cyclophilin D (CypD). Once opened, the MTP allows the release of pro-apoptotic proteins, such as cytochrome c and the apoptosis inducing factor into the cytoplasm which activates the apoptotic cascade.[2,33,34] Recently, a major transcription factor, Nrf2 (NF-E2-related factor 2), has been shown to protect neurons from toxic insults such as increases in intracellular calcium, OS, and mitochondrial dysfunction. Nrf2 interacts with the antioxidant response element, activating a major pathway that regulates phase II antioxidant response which includes expression of free

radical scavengers and cytoprotective enzymes.[35] In neurodegenerative diseases, Nrf2 expression has been shown to be decreased and its over-expression has been shown to protect against neurodegeneration and cell death.[35,36]

Neuronal cell death is a hallmark feature of neurodegenerative diseases. However, it is not clear as to whether neuronal cell death is a result of apoptosis or necrosis.[37–39] The disruption of calcium homeostasis and resultant opening of the MTP, as well as the neuroprotective effects of Nrf2 in diseases such as Alzheimer's and Parkinson's suggest apoptosis. Further research is needed to validate this theory. Although neurodegenerative diseases share the general features of increased OS and cell death, the specific mechanisms underlying these pathologies are quite different. The following neurodegenerative diseases of Alzheimer's, Parkinson's, and ALS will subsequently be discussed in detail.

Alzheimer's disease

AD is the most common neurodegenerative disease and presents with a progressive loss of memory as neurons especially in the cerebral cortex and hippocampus, atrophy, and die. The main risk factor for Alzheimer's disease is age; its incidence rate doubles every 5 years after the age of 65.[40] It is estimated that each year approximately 1300 new cases are diagnosed per 100 000 elderly people over 65 years of age.[40] While some studies show that the pathology is not necessarily a result of aging, its prevalence is expected to increase in the USA from 13.2 to 16.0 million cases in the mid-century due to the increasing life expectancy of the population.[40]

Alzheimer's disease is one the most common tauopathies. Tauopathies are a diverse group of neurodegenerative diseases that present with cognitive and motor impairments. They are associated with an accumulation of protein abnormalities (Tau) in the brain that results in oxidative damage, inflammation, and increases in intracellular calcium levels.[40,41] Two major characteristics of Alzheimer's are the intracellular aggregation of the Tau protein due to its hyperphosphorylation and the extracellular aggregation of amyloid beta peptides (Aβs).[41] Hyper-phosphorylated Tau is insoluble and forms paired helical aggregates that are cytotoxic.[41] Abnormal production, degradation, and aggregation of Aβs is also cytotoxic and is thought to be an important initiating factor of Alzheimer's and is referred to as the 'amyloid hypothesis'.[42] AD's pathology is characterized by synaptic dysfunction, nerve cell death, extracellular deposition of Aβs (forming senile plaques), and intracellular precipitation/aggregation of hyper-phosphorylated Tau (forming neurofibrillary tangles). The exact biochemical mechanisms of AD remain unknown, but much

attention has been given to the massive loss of the neurotransmitter acetylcholine (necessary for cognition and memory) and the possible implication of OS in this process.[43,44]

Excitotoxicity and OS-induced triggering of degenerative signaling, including activation of stress kinases such as JNK (c-Jun N-terminal kinases), are thought to have important roles in AD.[45] Activation of these pathways could be contributed to, in part, by Aβs role in the generation of ROS. Aβs have high-affinity binding sites for both Cu and Zn, and amyloid protein precursors (APPs) also bind these metals via N-terminal metal-binding domains. Cu ions bind to Aβ monomers via three histidine residues and a tyrosine, or via a bridging histidine molecule in aggregated Aβ. Cu has been shown to induce significant Aβ aggregation at mildly acidic conditions (pH 6.6) which reflects the likely microenvironment in AD neurophils.[2] Both Aβs and APPs have strong Cu-reductase activity, generating Cu^+ from Cu^{2+}. This reaction produces hydrogen peroxide as a by product. Cu^+ is also a potent mediator of the highly reactive hydroxyl radical ($OH^·$) and APP or Aβ associated Cu^+ may contribute to the elevated OS characteristic of the AD brain.[2] Aβs also may cause oxidation of non-saturated carbohydrate side chains of membrane lipids. This leads to the disintegration of neuronal membranes and ultimately cell death.[46] In addition to the direct induction of OS, Aβs can also indirectly generate an oxidative microenvironment via the induction of a local immune response. In fact, cellular mediators of inflammation are often found in post-mortem AD tissue.[47]

Parkinson's disease

PD is the second most common neurodegenerative disease. It presents with abnormalities in motor control and muscle rigidity as dopaminergic neurons in the substantia nigra (SN) atrophy and die.[48,49] The main risk factor for PD, as in Alzheimer's, is age. The estimated overall annual incidence rate is 12.3 per 100 000 and increases to 44 per 100 000 over the age of 50.[50] Although PD is typically age related and idiopathic, some atypical cases are caused by genetic mutations in genes that encode proteins associated with mitochondrial function.

Pathologically, PD is characterized by the death of dopaminergic neurons, increases in OS/damage, and mitochondrial dysfunction. These increases are normally caused by the accumulation and aggregation of alpha-synuclein within Lewy bodies.[51–53] Lewy bodies are abnormal intracellular aggregates of protein that develop inside nerve cells in PD and are mainly composed of alpha-synuclein. Over-expression of alpha-synuclein caused by gene multiplications is the major causative factor in PD suggesting that

alpha-synuclein accumulation is toxic.[52] However, DNA mutations in the alpha-synuclein encoding gene, parkinson protein 1 (PARK1), as well as other genes, such as parkinson protein 2 (PARK2), polymerase gamma (POLG), and phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) are also able to cause PD in atypical cases.[51] Point mutations in PARK1, which encodes the alpha-synuclein protein, cause the aggregation of this protein with resultant cytotoxicity and onset of PD. Alpha-synuclein is typically found in neuronal and glial cells in a linear soluble form and interacts directly with the inner mitochondrial membrane. It has been shown to inhibit mitochondrial complex I activity in the SN; therefore, it may be a major contributor to mitochondrial dysfunction and generator of ROS in PD.[51] Mutations in PARK2, which encodes the parkin protein that is a component of a multiprotein E3 ubiquitin ligase complex, are not associated with Lewy body formation but still cause dopaminergic cell death and onset of PD.[51] Mitochondrial DNA deletions in POLG, which encodes a catalytic subunit of the mitochondrial DNA polymerase, cause reduced dopamine transport and onset of PD.[51] Recessive mutations in the kinase domain of PINK1, which encodes the PINK1 protein, result in the abnormal phosphorylation of mitochondrial proteins, defective oxidative phosphorylation, increased OD, and onset of PD.[51]

Recently, monoamine oxidase B (MAO-B) has emerged as another possible component in the pathology of PD. MAO-B is bound to the outer mitochondrial membrane in neuronal and glial cells, and is able to degrade the neurotransmitter dopamine. In PD dopaminergic neurons in the SN selectively degenerate. MAO-B exacerbates this effect by degrading the neurotransmitter dopamine that is already deficient in this region; which, in return produces H_2O_2 and toxic aldehydes as a by-product of this degradation.[54] MAO-B is mainly localized in glial cells and is also able to oxidize the xenobiotic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to 1-methyl-4-phenyl-pyridinium which is a known neurotoxin that causes PD.[54] MAO-B levels have been shown to increase with age and in PD as well as other neurodegenerative diseases, and are associated with increases in the production of ROS.[53] In fact, transgenic C57Bl6 mice expressing human MAO-B within astrocytes at levels seen in advanced age was sufficient enough to produce significant neuronal death due to increases in ROS production and OD.[53] ROS produced by MAO-B can be released into the extracellular environment and can diffuse into neighboring cells. This can result in the accumulation of intracellular H_2O_2 within the terminals of dopaminergic neurons. This is followed by an accompanying increase in dopamine oxidation to dopaminochrome (DACHR), as well as selective mitochondrial complex I inhibition, and elevation in mitochondrial superoxide levels.[55]

Amyotrophic lateral sclerosis

ALS; also known as Lou Gehrig's disease is a neurodegenerative disease that involves the selective death of neurons in the cortex, brainstem, and spinal cord. This results in progressive paralysis and muscle atrophy.[56] The name of this disease reflects the different tissue compartments that are severely affected. In particular, 'amyotrophic' refers to the atrophy of muscle fibers and loss of muscle mass, 'lateral' refers to the nerve tracks that run down both sides of the spinal cord where many neurons affected by ALS are found, and 'sclerosis' refers to the scar tissue that remains following neuronal degeneration.[57] ALS has an incidence of 1–4 per 100 000 each year, and a prevalence of 4–6 per 100 000 worldwide. People of all races and ethnic backgrounds are affected, men more often than women, and mostly between 40 and 60 years of age.[58] ALS is epidemiologically classified into two forms sporadic (90–95%) and familial (5–10%).[59]

Pathologically, ALS is characterized by increases in OS, loss of mitochondrial membrane potential (Δ_{Ψ_m}) and changes in electron transport, formation of protein aggregates, altered Ca^{2+} homeostasis, excitotoxicity by AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor)/kainate receptos, and aberrant functioning of surrounding glial cells.[60–70] Since the discovery of missense mutations in the gene encoding the antioxidant enzyme Cu/Zn superoxide dismutase 1 (SOD1) in familial ALS, most ALS research has been directed toward elucidating this mechanism.[71] A major hallmark of ALS is the presence of intracellular protein inclusions. Which are mainly composed of aggregated SOD1 caused by mutations in the SOD1 gene.[72,73] In fact, aggregation of SOD1 in transgenic mice with mutations in the SOD1 gene was sufficient enough to cause ALS.[74,75] SOD1, which is predominantly a cytosolic protein, normally localizes within the intermembranous space (IMS) of the mitochondria; however, mutant SOD1 has been shown to accumulate on the outer membrane (OM) and matrix.[59,76–79] Mutant SOD1 aggregation in both the matrix and OM has been shown to increase ROS production resulting in morphological and functional abnormalities in mitochondria, and eventually neuronal cell death.[80–82] Targeting mutant SOD1 specifically to the IMS also resulted in mitochondrial dysfunction.[83,84] The targets of mutant SOD1 in mitochondria are not fully characterized, but defects in the activity of complex IV of the respiratory chain have been consistently described.[76,82,85,86] These defects can be attributed to impaired association of cytochrome *c* with the inner membrane, competition for mitochondrial copper supply between mutant SOD1

and complex IV, or inhibition by excess NO production.[62,87,88] ALS mediated by aggregated SOD1 is not strictly limited to neurons and has a major glial component as well. Forsberg *et al.*[70] found that aggregated SOD1 is also present in the nuclei of glial cells with mutated SOD1 and in sporadic and familial ALS that both lack such mutations. In one study, nuclear staining of aggregated SOD1 in glial cells was found in 59 out of 60 ALS patients investigated. This demonstrated the important role of glial cells in the dysfunction of motor neurons in ALS.[89]

Natural antioxidants and their neuroprotective effects

OS/damage is one of the most important characteristics of neurodegenerative diseases. Evidence supports the hypothesis that neuroprotection may be an achievable pharmacological target against neurodegenerative disorders; however, to date few effective compounds have been developed for clinical application and even fewer have been successful because of their toxicity and potential to cause cancer. On the other hand, the use of relatively safe antioxidant compounds found in the diet as a form of treatment in these disorders is attractive but limited by the difficulty in reaching an active concentration in the brain.[90] Natural antioxidants like polyphenols provide neuroprotective effects through a variety of biological actions, such as interaction with transition metals, inactivation of free radicals, modulation in the activity of different enzymes, and effects on intracellular signaling pathways and gene expression.[91,92] Several epidemiological studies suggest that diets rich in antioxidants play an important role in the protection against various pathologies. The main sources of

these molecules are found in fruits and vegetables and are associated with lower risks of cancer, heart disease, hypertension, neurodegenerative diseases, and stroke.[93–95]

Polyphenols are secondary plant metabolites that represent a broad group of compounds having aromatic rings and are characterized by the presence of one or more hydroxyl groups with different structural complexities. The most abundant class of phenolic compounds in plants are flavonoids, such as flavonols, flavones, isoflavones, anthocyanidins, etc. (Fig. 3). The most common dietary polyphenols in general are the flavonols (quercetin and catechin) as well as the non-flavoid compound resveratrol. Resveratrol (3,5,40-trihydroxystilbene) is a phytoalexin present in red wine and grapes. It has two phenolic rings connected by a double bond and has two isoforms *trans*-resveratrol and *cis*-resveratrol. Trans-resveratrol is the main focus of current research and is thought to be responsible for the French Paradox.[91] Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is a flavonol found in apples, tea, capers, and onions. Catechins are flavanol monomers comprising chemically similar compounds such as (+/−)-epicatechin, (+)-gallocatechin, (−)-epicatechin gallate (EGC), and (−)-epigallocatechin gallate (EGCG).[96] There are more than 50 different plant species and over 8000 phenolic compounds identified either in their single or pure molecular form or in specific proportions of differing plant extracts. Investigating the health benefits of these natural compounds is an enormous challenge to modern medicine.[97]

Green tea polyphenols are believed to be strong antioxidants against hydroxyl radicals, nitric oxide, and lipid oxidation.[98] They contain a number of
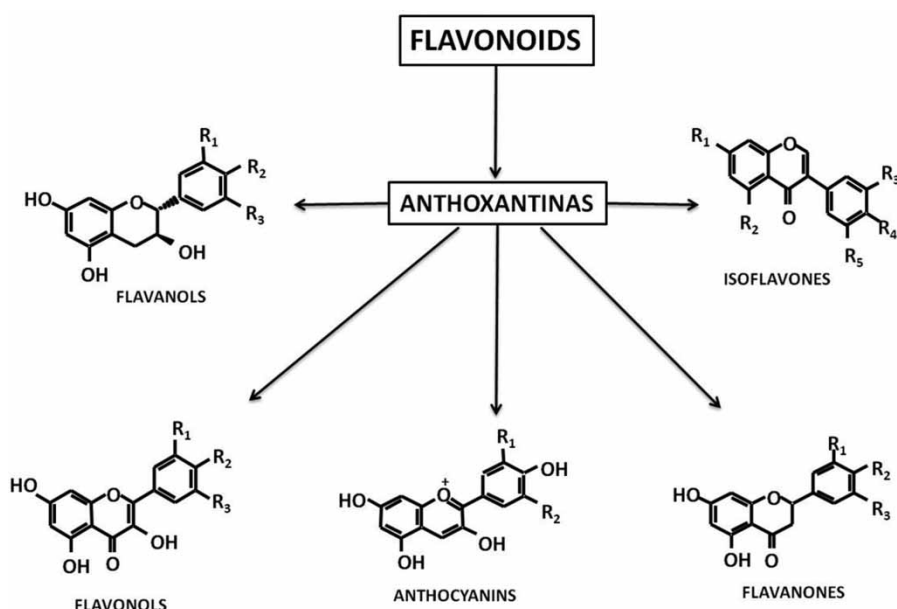

Figure 3 The subgroups of flavonoids.

bioactive chemicals and are particularly rich in flavonoids including catechins and their derivatives of which epigallocatechin-3-gallate (EGCG) is the main constituent. EGCG accounts for more than 10% of the dry weight extract, followed by (−-)-epigallocatechin (EGC), (−)-epicatechin (EC), and (−)-epicatechin-3-gallate (ECG).[99] These flavonoids have antioxidant potencies in the order of EGCG > ECG > EGC > EC.[100] Their free radical scavenging abilities relate to the gallate moiety esterified at position 3 of the C ring, the catechol group (3,4-dihydroxyl groups) on the B ring, and the hydroxyl group at positions 5 and 7 on the A ring. Moreover, the free radical scavenging property increases with the number of hydroxyl groups that the catechin possesses. For example, EGCG and EC possess eight and five hydroxyl groups, respectively, and the antioxidant activity of EGCG is higher than that of EC.

In neurodegenerative diseases, administration of green tea extracts reduced Aβ production/aggregation when APP/Aβ was over-expressed in mice and when APP/Aβ was over-expressed in neuron cell cultures through enhanced beta-secretase activity.[101] EGCG, the most important flavonoid extracted from green tea leaves, has been shown to reduce gamma and beta-secretase activity, attenuate the amyloidogenic pathway, reduce the presence of Aβ aggregation, and in return prevent neuron cell death in Alzheimer's disease.[102] Another study, using PC12 cells, demonstrated the protective effects of EGCG and extracts from grape skin on the neurotoxicity caused by Aβ.[103] Also of interest is the ability of catechins and epicatechins, that were extracted from grape seeds, to reverse the aggregation of tau in AD.[104] An alternative and putative mechanism for decreased aggregation of Aβ in neurons is the ability of certain polyphenols to interact with metals such as copper. It is known that aggregates of Aβ interact with copper and promote increases in ROS production.[105]

Other well-known polyphenols include Baicalin and Curcumin. Baicalin, an ancient Chinese herbal medicine, is another well-known flavonoid that is isolated from the Scutellaria baicalensis root (Huang Qin). Baicalin has been shown to inhibit the aggregation of Aβ and reduce the production of H_2O_2 and oxidative damage in SH-SY5Y cells.[106] Curcumin (diferuloylmethane), a non-flavonoid polyphenol, is derived from turmeric, the powdered rhizome of the medicinal plant *Curcuma longa Linn*. It has been used for centuries throughout Asia as a food additive and a traditional herbal remedy. Recent studies demonstrated that besides potent anti-oxidative and anti-inflammatory properties, curcumin also exhibits anti-amyloidogenic effects.[107] Curcumin binds amyloid directly and inhibits Aβ aggregation

preventing fibril and oligomer formation.[108] These anti-fibril effects of curcumin were also observed in studies involving alpha-synuclein in PD.[109] Other studies have shown that curcumin may also be able to increase Nrf2 expression and increase the neuroprotective effects in AD and PD.[110]

Conclusion

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS are age-related diseases that lead to protein aggregation, ROS production, OD, mitochondrial dysfunction, and cell death. Treatments (intranasal, intravenous, and oral) of these diseases with synthetic compounds in clinical trials have proven difficult due to their toxicity and ability to cause cancer. Therefore, treatments with natural antioxidants such as polyphenols through diet or dietary supplements have become an attractive alternative.

Clinical trials testing the efficacy of polyphenol dietary supplements in the treatment of neurodegenerative diseases remain scarce. At this time we are not aware of any clinical trials using polyphenols in the treatment of ALS or PD. The following are the current ongoing clinical trials using polyphenols in the treatment of Alzheimer's disease: Phase IV clinical trial, Effects of Dietary Interventions (including resveratrol) on the Brain in Mild Cognitive Impairment at Charité Universitätsmedizin Berlin directed by Dr Agnes Floeel; Phase III clinical trials, Randomized Trial of a Nutritional Supplement (resveratrol) in Alzheimer's Disease at the Mount Sinai School of Medicine directed by Dr Mary Sano, Pilot Study of the Effects of Resveratrol Supplement in Mild-to-Moderate Alzheimer's Disease at the Institute of the Study of Aging directed by Dr John Ringman; Phase II clinical trials, Curcumin in Patients with Mild to Moderate Alzheimer's Disease at the UCLA Medical Center directed by Dr John Ringman, and Efficacy and Safety of Curcumin Formulation in Alzheimer's Disease at the Jaslok Hospital and Research Centre directed by Dr Fali Poncha.

Polyphenols, both flavoids and non-flavoids, have proven to be effective in alleviating and protecting against the general mechanisms of neurodegenerative diseases in various cell culture and animal models. However, clinical trial research utilizing polyphenol dietary supplementation or a novel dosage form remains scarce. Much remains unknown about the bioavailability of polyphenols such as absorption after ingestion, effects of food matrix on absorption, metabolic fate in the liver, and tissue uptake. Also, very few circulating metabolites of polyphenols have been researched and identified. Compounding this issue is polyphenol's poor absorption and rapid

elimination from the plasma. Given the rapid plasma elimination of polyphenols, a novel intravenous dosage form would be of great interest. Future research is needed to further elucidate the polyphenol neuroprotective mechanisms and to identify which classes and combinations of polyphenols have the most efficacies. The further characterization of pathways involved in polyphenol bioavailability and transport after consumption is also of importance.

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