Chapter 6
Recent Advances in Application of Dietary Polyphenols to Treat Age-Related Neurological Disorders

Prachi Vibhute, Akshaya Radhakrishnan, and Jeyachandran Sivakamavalli

Abstract One of the main causes of synaptic damage and impaired neural transmission in numerous neurodegenerative disorders is the progressive buildup of misfolded amyloid proteins in intracellular and extracellular areas. Effective therapies for these illnesses are still unavailable, although they are nevertheless the subject of intense research. Despite decades of study, just a few synthetic chemicals, small molecules, and medicines have been found to prevent amyloid protein aggregation and reduce their neurotoxic effects. Antioxidants, particularly those derived from food, have been proposed as potential medicines for the prevention and treatment of Alzheimer's disease in recent years. Polyphenols are known to lower the risk of neurological disorders such as Alzheimer's disease (AD), stroke, multiple sclerosis (MS), Parkinson's disease (PD), and Huntington's disease (HD) through reducing oxidative stress. Polyphenols have the ability to address the genesis of neurological diseases by attenuating their complicated physiology by simultaneously regulating several therapeutic targets. Several research published in recent years aimed to verify sensitive and reliable translational techniques for mechanistically characterizing brain bioavailable polyphenols as disease-modifying drugs to help prevent the onset of Alzheimer's disease and other neurodegenerative disorders. Several research groups from around the globe with expert knowledge in Alzheimer's disease, plant biology, nutritional sciences, and botanical sciences have published high-quality study results that have finally provided the necessary evidence that polyphenols and their metabolites, which can be found in a variety of foods, can help to prevent Alzheimer's disease. The studies mentioned in this review article back up the findings of recent research that have had a significant influence on neurodegenerative disorders by giving crucial information on polyphenols' protective functions. Despite the fact that current polyphenol research has had minimal influence on clinical practice, there is significant evidence and testable hypothesis that they can contribute to therapeutic advancements and therapeutic discovery in the field of age-related neurological diseases.

P. Vibhute · A. Radhakrishnan · J. Sivakamavalli (✉)
PG & Research Department of Biotechnology & Microbiology, National College, Tiruchirappalli, Tamil Nadu, India
e-mail: drjsvalli@nct.ac.in

P. Elumalai, S. Lakshmi (eds.), *Functional Foods and Therapeutic Strategies for Neurodegenerative Disorders*, https://doi.org/10.1007/978-981-16-6703-9_6

Keywords Polyphenols · Neurodegenerative disease · Alzheimer's disease · Multiple sclerosis · Parkinson's disease

Abbreviations

AD	Alzheimer's disease
BDPP	Bioactive dietary polyphenol preparation
EGCG	Epigallocatechin-3 gallate
GPx	Glutathione peroxidase
GR	Glutathione reductase
HD	Huntington's disease
JNK	c-Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
MCI	Mild cognitive impairment
MS	Multiple sclerosis
NFkB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PD	Parkinson's disease
Syn	α-Synuclein

6.1 Introduction

Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease, and other neurodegenerative illnesses are only a few examples. Because their instances are sporadic, determining the cause of these diseases and preventing them are difficult. Many neurological disorders and age-related degenerative processes have been linked to oxidative stress. Neurodegenerative disorders have a complicated etiology involving a complex combination of hereditary and environmental variables. The bulk of these instances are of an environmental or sporadic nature. The most prevalent neurodegenerative illnesses are Alzheimer's disease (AD) and Parkinson's disease (PD). They are complex, progressive, age-related, and genetically and environmentally affected. Despite the fact that they are public health issues that have been extensively researched, there are no viable remedies. Currently, treatments are only symptomatic and aimed at improving patients' quality of life (Przedborski et al. 2003). Furthermore, there are no diagnostic techniques for early diagnosis of these illnesses, which share several clinical characteristics, particularly at the start. Specific proteins have been linked to the diseases, but it is unknown when and how they lose their function and become abnormal and toxic. Several routes of cellular malfunction have been put forward to explain the disease toxicity; however, the pathological significance of the proteins implicated is still debated. Personalized therapies and targeted medicines are by far the most efficient treatment methods. Alternative pharmacological therapies and natural compounds,

particularly those linked with the Mediterranean diet, such as polyphenols, have sparked fresh attention in the recent decade. Polyphenols' surprising advantages and broad range of characteristics imply that further research is needed to have a better understanding of their mechanism of action and to employ them in further successful treatments (Bagetta et al. 2020).

Because it uses so much oxygen for energy and has so few antioxidant defense enzymes, the brain is particularly sensitive to oxidative damage, especially as it ages. Furthermore, the membranes of brain cells contain very high levels of polyunsaturated fatty acids (PUFAs). Neurons are particularly prone to toxic chemicals and to damage caused by ischemia/stroke, seizures, and other excitotoxic injuries among the many kinds of brain cells (Milatovic et al. 2009). Lipid peroxidation (oxidative damage to lipids) is linked to a gradual loss of membrane integrity, a decrease in mitochondrial membrane potential, and an increase in plasma membrane permeability to Ca^{2+}. Carbonyl and nitrosylated derivatives are formed when proteins are damaged by oxidation. In addition, ROS damage to DNA causes nuclear condensation and changes in gene expression. Different reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, and hydroxyl and peroxyl radicals, are generated in cells under normal and pathological circumstances, according to research (Valls et al. 2005). Oxidative damage to DNA, proteins, and lipids occurs when the rate of ROS production surpasses the capability of antioxidant defense. Oxidative stress has been linked to neuronal cell damage in the central nervous system (CNS) in a variety of disease conditions. The term "nitrosative stress" has lately been coined to describe cellular damage caused by reactive nitrogen species (RNS), which would include nitric oxide (NO) and its derivative products such as peroxynitrite and nitroxyl anion (Klatt and Lamas 2000). Oxidative and nitrosative stresses are both involved in the pathology of many neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD).

In in vitro and in vivo models of neurodegeneration, many antioxidant substances produced from natural products (nutraceuticals) have shown neuroprotective effects: (1) flavonoid polyphenols, such as epigallocatechin 3-gallate (EGCG) and quercetin; (2) non-flavonoid polyphenols, such as curcumin and resveratrol; (3) phenolic acids or phenolic diterpenes, such as rosmarinic acid or carnosic acid; and (4) organosulfur compounds, such as isothiocyanate, L-sulforaphane, and thiosulfinate (allicin) (Kelsey et al. 2010). They directly scavenge free radicals or indirectly boost endogenous antioxidant defenses by activating the nuclear factor erythroid-derived 2-related factor 2 (Nrf2) transcription factor pathways, for example. The intrinsic free radical scavenging activities of these nutraceutical antioxidants suggest that they may have potential utility in mitigating neuronal oxidative stress and neurodegeneration as shown in the Fig. 6.1. Other mechanisms of action of these compounds include modulation of signal transduction cascades or effect on gene expression (Tuñón et al. 2009). The following sections will be discussing the mechanism of action of polyphenols to help in treating neurodegenerative disorders.

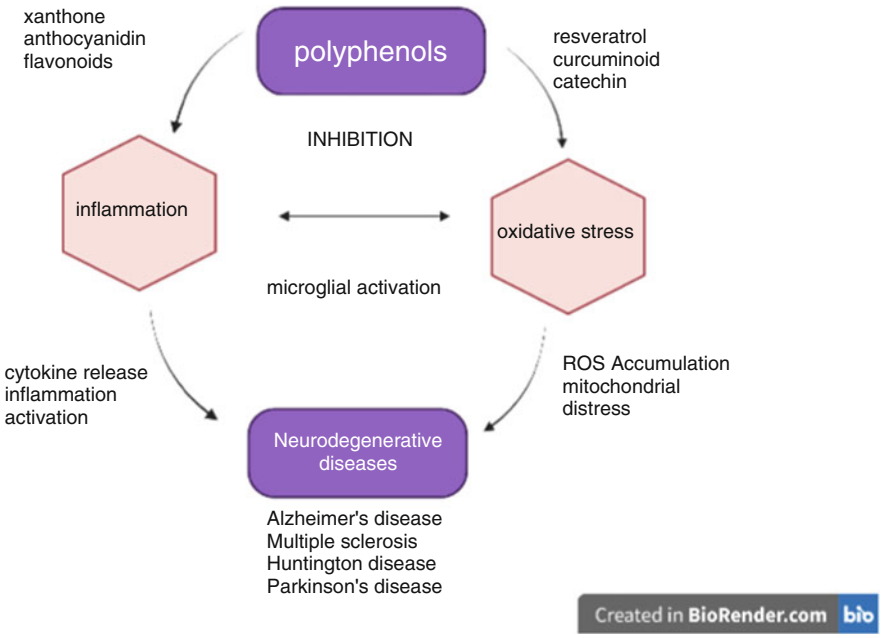

Fig. 6.1 Role of polyphenols in neurodegenerative disease treatment

6.2 Introduction to Neurodegenerative Disorders

6.2.1 Alzheimer's Disease (AD)

Alzheimer's disease is marked by a progressive decrease of cognitive function, memory loss, and behavioral abnormalities. A synaptic deficiency in the neocortex and limbic system, neuronal loss, white matter loss, astrogliosis, microglial cell proliferation, and oxidative stress are all common symptoms of the illness. The appearance of intracellular flame-shaped neurofibrillary tangles with extracellular plaques in the brain is a pathological marker of Alzheimer's disease (Stutzmann 2007). The Tau protein, in a hyperphosphorylated state, is the most common cause of tangle formation in the perinuclear cytoplasm. The plaques are caused by the accumulation of amyloid-β-peptide (Aβ) in a filamentous form throughout time. The neuritic plaques range in size from 10 to more than 120 μm in diameter. The procedures for determining the pathology's diagnostics have been standardized. The number and degree of compactness of neuritis amyloid plaques and neurofibrillary tangles are discussed. As a result of their location and development, AD aggregates can be categorized as positive or negative lesions. Amyloid plaques and neurofibrillary tangles, neuropil threads, and dystrophic neurites, all of which are fundamentally generated by hyperphosphorylated Tau, are typical positive lesions. Neurons and neuropil threads are lost in the negative lesions (Selkoe 1991).

6.2.2 Parkinson's Disease (PD)

Motor symptoms such as bradykinesia, stiffness, resting tremor, and instability are common in people with Parkinson's disease. Because there is no conclusive test for the diagnosis of Parkinson's disease, the emergence of these clinical symptoms is critical for the illness's early treatment. The loss of dopaminergic neurons in the *Substantia nigra pars compacta* and the deposition of intraneuronal proteinaceous clumps, primarily formed of α-synuclein (Syn), known as Lewy bodies and Lewy neurites, are hallmarks of Parkinson's disease (Taylor and Saintcyr 1995). Syn was also discovered in the Lewy body form of Alzheimer's disease and multiple system atrophy pathological inclusions. Syn inclusions are also seen in other neurodegenerative illnesses known as synucleinopathies, including Down's syndrome, progressive autonomic failure, and familial and sporadic Alzheimer's disease. Shahmoradian and colleagues have shown that Lewy bodies are produced not only by Syn deposits but also by clusters of lipid vesicles. These significant findings show a link between Syn–lipid interaction and neurodegeneration (Halliday and McCann 2010).

6.2.3 Multiple Sclerosis (MS)

MS is a systemic illness that affects the central nervous system's gray and white matter. Inflammatory and degenerative mechanisms occur simultaneously, and the balance between them determines whether the illness is relapsing–remitting or progressive. It is unclear if basic progressive MS is a distinct disease entity or just a disease phenotype without high-grade inflammatory processes. The same dilemma applies to very active MS patients with tumefactive lesions, and the question is if there is a molecular key that defines whether an immune response is overwhelming or subtle (Stadelmann 2011). The existence of localized white matter lesions, characterized by initial demyelination with partial preservation of axons and reactive astrocytic scar formation, was originally used to describe its pathophysiology. Although, in comparison to full demyelination, axons are relatively well maintained inside the lesions, they are nonetheless damaged, and axonal loss has been proven to be a key predictor of persistent neurological impairment in MS patients. When patients have clinical relapses and remissions in the early stages of the disease, inflammatory demyelination causes localized plaques to develop, which are mostly seen in the white matter. Additional pathology is found in later stages of the disease, especially in individuals with secondary or main progressive disease, such as extensive demyelination in the cerebral and cerebellar cortex, as well as diffuse degenerative alterations throughout the white and gray matter (Lassmann 2018). Patients with long-term severe illness eventually have significant brain and spinal cord atrophy, as well as widespread tissue loss and cerebral ventricle dilation. While the illness begins with inflammatory-driven localized demyelinating lesions that

develop around tiny drainage veins in the white matter, it eventually progresses to widespread neurodegeneration that affects the whole CNS (Lassmann et al. 2012).

6.2.4 *Huntington's Disease (HD)*

Huntington's disease (HD) is a neurological illness that causes mobility problems, cognitive decline, and mental symptoms. A (CAG)n trinucleotide repeat expansion near the 5′ end of a gene that codes for the huntingtin protein causes it as listed in the Table 6.1 (van der Burg et al. 2009). The repetitions induce illness by providing a new detrimental function on huntingtin, which is translated into an abnormally enlarged polyglutamine tract. The pathophysiology of HD is characterized by the neuronal loss that is selective, with the striatum and deeper layers of the cerebral cortex suffering the most. The development of intraneuronal inclusions or aggregates is linked to the illness. With a clinical course of >15–20 years, HD causes catastrophic brain atrophy and death (Vonsattel and DiFiglia 1998). The striatal medium spiny neurons (MSNs) of the brain appear to be particularly susceptible in HD, while other brain areas may also be impacted. GABAergic MSNs are found in the striatum and project to the substantia nigra (striatonigral) and globus pallidus (striatopallidal). Even though the specific causes for this selective susceptibility and loss of striatal MSNs are unknown, it has been observed that HD patients lose around 88% of their striatal neurons as compared to healthy persons (Holley et al. 2018).

6.3 Introduction to Polyphenols

Polyphenols are substances having at least two hydroxyl groups linked to one or more phenyl rings. Thousands of polyphenolic compounds exist in plants, each with several alternative double bonds, hydroxyl groups, and more than one phenyl ring.

Table 6.1 Age-associated neurodegenerative diseases and their associated protein

Disease.	Affected region	Protein aggregated	Deposition	References
Alzheimer's disease	Cerebral cortex, hippocampus	Amyloid-beta, tau	Intracellular tangles and extracellular plaques	Selkoe (1991)
Huntington's disease	Striatum, cerebral cortex	Huntingtin	Intracellular nuclear inclusions	Ghosh and Tabrizi (2018)
Parkinson's disease	Substantia nigra	Alpha-synuclein	Intracellular cytoplasmic inclusions	Taylor and Saintcyr (1995)
Multiple sclerosis	CNS: Gray and white matter	Amyloid precursor, tau	Cerebrospinal fluid lesions and plaques	Stadelmann (2011)

Table 6.2 Major polyphenols and their characteristics (Han et al. 2007)

Polyphenols	Dietary form	Chemical nature	Source of availability
Flavanols	Catechin, epicatechin EGCG	Methyl sulfate conjugates; EGCG in unconjugated forms	Teas, apple pears, chocolate
Curcuminoid	Curcumin	Desmethoxycurcumin, bismethoxycurcumin	Turmeric
Anthocyanidins	Cyanidin, malvidin	Glucosides	Red, blue, purple berries
Stilbene	Resveratrol	Glucuronides, sulfate conjugates	Purple grape, redwine, peanut
Dihydrochalcone	Aspalathin	2,3,4,4-pentahydroxy-3-C-β-d-glucopyranosyl dihydrochalcone	Legumes
Xanthones	Xanthones, mangiferin, and isomangiferin	Tricyclic aromatic system	Honeybush tea

Anthocyanins, flavanols, flavones, isoflavones, stilbenes, and lignans are only a few examples of plant-derived polyphenols (Scalbert et al. 2005). Polyphenols are secondary metabolites that are considered to protect plants from radiation, infections, and other stresses. In edible plant components such as fruit, leaf, stem, root, and seed, over 500 polyphenolic chemicals have been discovered of which, major are listed in the Table 6.2. Preclinical, clinical, and epidemiological research shows that a plant-based diet, with a concentration on fruits and vegetables, decreases the risk of neurodegenerative disorders substantially. Polyphenolic chemicals found in edible plants are a vital class of micronutrients that contribute to the health advantages of a diet rich in fruits and vegetables (Dai and Mumper 2010). Polyphenols have a lot of antioxidant characteristics, including the capacity to scavenge free radicals and boost the production of antioxidant enzymes, according to a lot of data. Polyphenols have also been demonstrated to reduce the production of pro-inflammatory cytokines and inhibit the inflammatory cascade. Dietary polyphenols' antioxidant and anti-inflammatory properties lower tissue damage risk and contribute to health benefits in age-related chronic illnesses (Oliviero et al. 2018). Polyphenols have been shown to affect cellular signaling mechanisms and signal transduction pathways associated with oxidative stress, redox modulation, the inflammatory cascade, cell proliferation and migration, and a variety of other processes linked to the pathogenesis and progression of chronic diseases (Kang et al. 2019). Several important dietary polyphenols have been studied in preclinical in vitro and in vivo models of chronic illnesses during the last decade. Green tea catechins and blacktea theaflavins (found in green tea and black tea), curcuminoids (found in the curry spice turmeric), anthocyanins (found primarily in berries), and resveratrol (found in red wine, grapes, and peanuts) have all been studied for their therapeutic potential in the treatment of age-related chronic diseases (Hano and Tungmunnithum 2020).

6.3.1 Tea Polyphenols

After water, tea, made from the leaves of the *Camellia sinensis* plant, is the most frequently consumed beverage on the planet. The main difference between white, green, oolong, and black teas is the degree of processing throughout the production process, which largely consists of drying and fermenting. The most significant polyphenols in tea are catechins and theaflavins, whose amounts vary according to the degree of oxidative fermentation (Xing et al. 2019). Catechins are found in the greatest concentrations in nonfermented white and green teas, which dimerize to create theaflavins when oxidized. Black tea, which is made by fermenting tea leaves, is high in theaflavins, which are orange-red pigments that give it its color. Oolong tea is a hybrid of green and black teas that have been partially fermented (Kamat et al. 2008). Along with other catechins and theaflavins, epigallocatechin-3 gallate (EGCG), the most famous and well-known tea polyphenol, has been widely investigated in preclinical models of chronic illness and clinical trials. EGCG and other tea polyphenols have been found to have potent antioxidant and anti-inflammatory properties, as well as modulatory action for a variety of disease progression signaling pathways (Williams et al. 2004).

6.3.2 Curcuminoids

Turmeric is a rhizome (*Curcuma longa*) that grows in tropical South Asia and is also known as "Indian saffron." Turmeric's therapeutic properties are owed to the intensely yellow curcuminoid polyphenols curcumin, desmethoxycurcumin, and bisdesmethoxycurcumin, which have shown therapeutic potential in a variety of age-related chronic ailments, including autoimmune, cardiovascular, cancer, and neurodegenerative diseases, such as Alzheimer's and Parkinson's disease (Sharma et al. 2005). Curcumin, the main curcuminoid found in turmeric, is one of the most researched dietary compounds, with strong antioxidant and anti-inflammatory effects as well as the capacity to influence a variety of signaling pathways (Tønnesen and Karlsen 1985).

6.3.3 Anthocyanins

Anthocyanins are a category of water-soluble pigments found in a variety of flowers, fruits, and vegetables. They are present in large amounts in several popular berry fruits of the genus *Vaccinium*, as well as many other genera such as bilberry, blackberry, blueberry, cranberry, lingonberry, mulberry, raspberry, and strawberry, as well as cherries and currants, and are responsible for the blue and purple color of berries. Pomegranate (*Punica granatum*), a "wonder fruit," and chocolate both

contain anthocyanins (Francis 1982). Among the most frequent dietary anthocyanins are cyanidin, delphinidin, malvidin, peonidin, pelargonidin, and petunidin, to name a few. Many epidemiological studies have highlighted the health advantages of anthocyanin-rich dietary components, whose potent antioxidant, anti-inflammatory, and therapeutic activities have recently been studied (Farzaei et al. 2018).

6.3.4 Resveratrol

Resveratrol, a stilbene polyphenol found in several dietary and nondietary plant sources, is classified as a phytoalexin, synthesized in response to bacterial and fungal attack. Resveratrol is also produced in response to several environmental stresses, including ultraviolet (UV) radiation (Tian and Liu 2020). Some of the major dietary sources of resveratrol are berries, grapes, red wine, and peanuts. Resveratrol is a widely studied molecule and is most well known as the agent responsible for the "French paradox": a phenomenon whereby the consumption of red wine is suggested as the reason why the French suffer from a comparatively low incidence of cardiovascular disease despite having a diet rich in saturated fats (Darvesh et al. 2017). Resveratrol is a strong antioxidant and anti-inflammatory drug that has been proven to extend longevity in preclinical and clinical trials in a variety of oxidative stress and inflammation-related illnesses, including cancer, cardiovascular disease, infections, and neurological diseases (Das and Das 2007).

6.3.5 Dihydrochalcones

The plant Rooibos (*Aspalathus linearis*) belongs to the legume family and is only found in a tiny area of South Africa's Western Cape. Its dried and fermented leaves and twigs are used to produce herbal tea, which has been popular in the area for generations and is now exported and enjoyed worldwide (Street and Prinsloo 2013). The dihydrochalcones aspalathin (2,3,4,4-pentahydroxy-3-C-β-d-glucopyranosyl dihydrochalcone) and its structural homolog nothofagin are responsible for rooibos' antioxidant action (differing only in that it lacks the A ring catechol group) (Snijman et al. 2009). Using the thiobarbituric acid reactive substances (TBARS) test, Inanami et al. investigated the effect of long-term (>20 months) administration of rooibos extract on lipid peroxidation in the rat brain. Increased lipid peroxidation is significantly linked to AD and aging in humans, as previously mentioned. Lipid peroxides were found to be substantially greater in the frontal and occipital cortex, the hippocampus, and the cerebellum of control groups of 24-month-old rats compared to juveniles in a research study by Inanami and coworkers (aged 5 weeks). Surprisingly, the signal intensities for age-related markers in the frontal cortex, hippocampus, and cerebellum of rooibos-treated rats matched those of 5-week-old rats in an additional MRI study by the same authors, but the same areas in untreated 24-month-

old rats showed significant age and lipid peroxidation-related elevation of these markers (Darvesh et al. 2010). As a result, these researchers conclude that age-related accumulation of lipid peroxides in the brain, which was closely correlated with morphological changes seen on MRI, revealed that chronic rooibos administration prevented age-related accumulation of lipid peroxides in several regions of the rat brain (Inanami et al. 1995).

6.3.6 Xanthones

The genus *Cyclopia* includes a number of shrubs native to the Cape Fynbos area of South Africa, the most common of which is *Cyclopia intermedia,* often known as the honeybush shrub. Honeybush herbal tea, which is extensively drunk in South Africa, has been made from this plant for decades (McKay and Blumberg 2007). The honeybush has yielded many polyphenols, including the xanthones mangiferin and isomangiferin, as well as the flavanones hesperidin and eriocitrin. Mangiferin has been the most extensively investigated of these substances in paradigms relating to the underlying pathophysiological processes of Alzheimer's disease. Mangiferin protected mouse brain against oxidative damage caused by 12-O-tetradecanoylphorbol-13-acetate (TPA), according to Sánchez et al. In addition, when compared to TPA controls, mangiferin provided significant (22%) protection against DNA fragmentation in the brain and reduced lipid peroxidation in brain homogenates by 39% (Matkowski et al. 2013). Gottlieb et al. found that in the presence of submicromolar quantities of mangiferin, neuronal cell death caused by glutamate in in vitro cell cultures was reduced. Receptor-mediated calcium influx was reduced, oxidative stress was reduced, and apoptosis was significantly reduced in these cultures (Gottlieb et al. 2006).

6.4 Polyphenols and Neurodegeneration

6.4.1 Neuroprotective Activity

NDs are a diverse set of diseases defined by post-mitotic neuronal cell malfunction and/or gradual loss in the central or peripheral nervous systems. Cognitive decline, dementia, motor irregularities, sleep problems, and behavioral and psychiatric disorders are the most common clinical manifestations of neurodegeneration. The buildup of aberrant, misfolded, and aggregated proteins; mitochondrial dysfunction; inflammation; oxidative stress accumulation; improper neural transport; impairment of the autophagic process; and change in proteasome activity are all prevalent cellular and molecular processes in NDs. NDs are incurable, progressive, and highly debilitating illnesses that pose a major burden in terms of human suffering and healthcare expenditures. The challenge for physicians and researchers is to develop

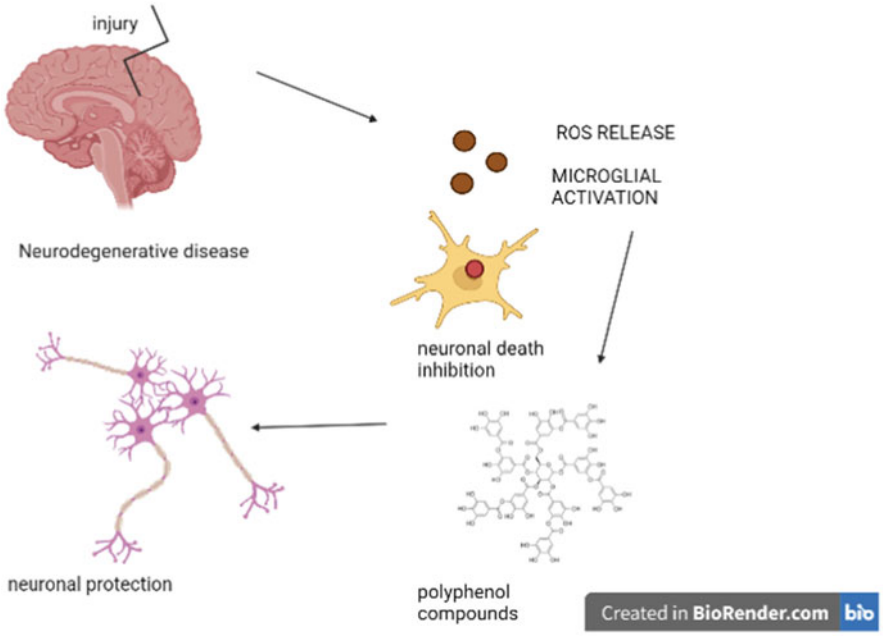

Fig. 6.2 Neuroprotective mechanism of dietary polyphenols

new medications to slow down neurodegeneration and enhance their patients' quality of life due to a lack of effective treatments. Increased cellular oxidative stress plays a significant part in the main etiologies of NDs, in addition to risk factors such as genetics and environmental influences (Tsuji 2002). Polyphenol consumption in the diet has been shown to reduce cellular oxidative stress and is a viable method for ND prevention. Polyphenols inhibit free radical damage by interacting with the hypoxia-inducible factor 1-alpha (HIF-1α) pathway, modifying production of protective genes against oxidative stress, regulating ROS via engaging with oxidative pathways, and scavenging metal ions. Metal ions (Fe^{2+}, ZN^{2+}, Cu^{2+}) accumulate in certain brain areas of ND patients, causing oxidative stress, which can be chelated by a wide range of polyphenols as shown in the Fig. 6.2. These chemicals, for example, appear to work by complexing transition divalent metal ions, resulting in a decrease in the quantity of iron and its accumulation (Shoval et al. 2008).

Polyphenols' anti-inflammatory properties have been linked to a reduction in the risk of neurodegeneration. These chemicals can regulate the expression of pro-inflammatory genes such nitric oxide production, lipoxygenase, cyclooxygenase, chemokines, and numerous cytokines, mostly through NFkB and MAPK signaling. Curcumin has been found to suppress NFkB signaling, which results in chemokine and Aβ aggregate production being reduced (Korkina et al. 2011). Similarly, resveratrol can reduce A-mediated microglial inflammation (a hallmark of Alzheimer's disease) through a mechanism that involves the Toll-like receptor

4 (TLR4)/NF-kB/signal transducers and activators of transcription (STAT) signaling cascade, and EGCG can prevent amyloidogenesis by inhibiting neuroinflammatory cytokines released by astrocytes (Rahimifard et al. 2017).

Other processes can be attributed to polyphenol compounds' neuroprotective effects, one of which is the decrease in amyloid-beta (Aβ) aggregates and/or fibril development (a hallmark of AD). Curcumin, resveratrol, and EGCG have been shown to have a positive impact on direct disruption of β-pleated sheets in several in vitro experiments (Udhayakumar 2020). Polyphenols, in particular, appear to bind to diverse surface regions of the β-sheet structure, causing a variety of consequences, including the formation of short, nontoxic oligomers.

Polyphenols interact with various pathways engaged directly or indirectly in the neurodegenerative process, in addition to the processes mentioned above. They are particularly important in signaling pathways involved in survival, cell proliferation, apoptosis, and autophagy. Polyphenols impact cellular function in this way by changing the phosphorylation state and expression levels of proteins involved in the phosphoinositide 3-kinase (PI3K), Akt/protein kinase B (Akt/PKB), tyrosine kinases, and protein kinase C (PKC) signaling pathways. Protein kinase A (PKA), PKC, topoisomerase, mitochondrial ATPase, and the benzodiazepine binding sites of type A gamma-aminobutyric acid (GABA-A) receptors are all possible targets for flavonoids. Several protein kinases have also been found to be inhibited by resveratrol, and EGCG is shown to interfere with the PKC signaling pathway. Several studies have highlighted the importance of the PKC signaling route in regulating critical molecular processes involved in associative memory storage, as well as how a defect in the PKC signaling pathway plays a key role in the pathophysiology of NDs (Ajami et al. 2017).

The structure–activity connection of polyphenolic compounds is another important factor to consider when addressing their neuroprotective effects. The structure–activity connections linking the physiological actions of antioxidants, such as polyphenols, to their compositions and structures have received a lot of attention. Lu and colleagues investigated the structure–activity connection for various gallic acid derivatives' antioxidant activity in an in vitro liposome system, as well as their neuroprotective efficacy against 6-hydroxydopamine-induced stress in human neuroblastoma cells. The study found that polyphenolic chemicals' ability to scavenge free radicals and their hydrophobic characteristics, which allow them to easily penetrate cell membranes and reach their targets, are both critical for their neuroprotective impact against oxidative damage. More recently, an interesting research study used H_2O_2-scavenging activity and 1,1-diphenyl-2-picrylhydrazyl (DPPH)-scavenging activity tests to evaluate the antioxidant potential of certain polyphenolic compounds (Youdim and Mandel 2012). The findings revealed that the H_2O_2-scavenging activity of phenolic molecules is strongly influenced by the chemical structure of the molecule, as well as the type, number, and position of the active group (OH or NH_2) and the kind, number, and position of the substituted group. The combination of an amino group and an electron donor at the ortho or para position has a detrimental influence on the scavenging activity of polyphenolic compounds, according to the study. Similar to the number of active groups, the

DPPH-scavenging activity is proportional to the number of active groups; hence, more active compounds contain more than one active group (Ingale and Kasture 2014).

In vivo studies on numerous animal models have also revealed the neuroprotective benefits of curcumin, resveratrol, and EGCG. Mansouri et al. looked into the neuroprotective benefits of intraperitoneally administered curcumin against homocysteine-induced neuronal damage in a rat model of Parkinson's disease. The findings revealed that homocysteine had neurotoxic effects on dopaminergic neurons in the substantia nigra and curcumin therapy decreased apoptosis and alleviated behavior symptoms. In a *Drosophila melanogaster* model of HD, similar results were obtained (Ataie et al. 2010). Curcumin therapy dramatically reduces neuronal motor dysfunction by reducing cell death, according to researchers. Ishrat and colleagues established the efficiency of curcumin treatment in preventing cognitive deterioration in a rat model of sporadic dementia of the Alzheimer's type. The hippocampus and cerebral cortex of treated rats showed a substantial improvement in cognitive impairments, as well as a reduction in glutathione peroxidase (GPx), glutathione reductase (GR), and reduced glutathione (GSH) levels, and an increase in choline acetyltransferase (ChAT) activity. According to findings from a study done in a mouse model of HD, resveratrol therapy improved motor coordination and learning while also increasing the expression of mitochondrial-encoded electron transport chain genes. In a rat model of Alzheimer's disease, resveratrol has been shown to protect the brain against A-induced damage (Ishrat et al. 2009). Research on bioactive dietary polyphenol preparations found that resveratrol's neuroprotective benefits were linked to a decrease in inducible nitric oxide synthase (iNOS) levels and lipid peroxidation, as well as an increase in heme oxygenase-1 synthesis (HO-1). Karuppagounder and colleagues published similar findings, demonstrating that resveratrol can reduce plaque development in a brain-specific area in a mouse model of Alzheimer's disease. This positive impact on A was linked to a reduction in brain glutathione and a rise in cysteine, which is a precursor to glutathione.

Xu et al. have investigated the neuroprotective effects of EGCG in a mouse model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD. By decreasing oxidative stress and modulating the iron-export protein ferroportin in the substantia nigra, EGCG alleviated MPTP-induced neurotoxicity. In a mouse model of Alzheimer's disease, the effects of EGCG on neuroinflammation and amyloidogenesis were investigated (Xu et al. 2020). The researchers discovered that EGCG therapy reduced memory impairment and neuronal cell apoptosis caused by lipopolysaccharide (LPS), as well as enhanced the production of tumor necrosis factor-alpha (TNF-1α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6). He and colleagues used an AD animal model to show that EGCG protects against neurodegeneration by lowering the levels of the amyloid precursor protein (APP) and Aβ in the hippocampus of afflicted mice. Overall, the data support the idea that dietary polyphenols, which primarily protect against Aβ plaque development, oxidative stress, and inflammation, can help postpone or prevent neurodegeneration (Rehman et al. 2021).

6.5 Advances in Application of Dietary Polyphenols to Treat Age-Related Neurological Disorders

6.5.1 Polyphenol Combination Therapy as a Novel Technique for Delaying the Onset of Alzheimer's Disease in People with Mild Cognitive Impairment

MCI is described as a syndrome characterized by subjective and/or objective evidence of cognitive impairment but no (or minimal) evidence of functional decline. Amnestic MCI (memory impairment) and nonamnestic MCI (nonmemory impairment) are two subtypes of MCI (affecting other cognitive domains only). Individuals with amnestic MCI are at a high risk of acquiring incident AD, and the majority of them have a high amyloid burden in their brains. Because people with MCI are by definition functioning well, finding therapies to prevent their development to dementia (secondary prevention of dementia) would be a significant public health benefit. There is presently no FDA-approved medication for secondary prevention of MCI, and trials of current Alzheimer's treatments have failed horribly. MCI is a risk group, not a disease state, and many people with MCI do not develop dementia or Alzheimer's disease; these people are unlikely to have a brain disease. Given these findings, it is especially critical that an intervention be reasonably safe and noninvasive (Lissek and Suchan 2021). The majority of existing interventions in this sector are cognitive or behavioral, with only a few medication trials, the most advanced of which being intranasal insulin, which is being investigated based on ideas that are similar to ours. MCI patients usually possess metabolic risk factors such as insulin resistance and prediabetes, putting them at an increased risk of cognitive deterioration (Biessels et al. 2014).

BDPP (bioactive dietary polyphenol preparation) is a novel nutraceutical combination that combines three bioactive and commercially available polyphenol products (Concord grape juice, grape seed extract, and resveratrol) to provide three selective, bioactive, polyphenol-rich dietary preparations to simultaneously target multiple AD pathogenic targets, as well as metabolic syndrome markers (primarily through resveratrol action). Each of the BDPP components has its own mode of action against AD pathogenic pathways, as we will go over in more detail below. As a result, when compared to individual BDPP components, BDPP application provides a more comprehensive coverage of AD pathogenic targets, making it a more effective method for treating individuals with early AD and prediabetes. They discovered that BDPP addresses amyloid burden, synaptic plasticity, and cognition in animal models of Alzheimer's disease and metabolic syndrome in current investigations. Those with prediabetes who have MCI are at a higher risk of developing Alzheimer's disease. This nutraceutical's benefits include a low risk of side effects, oral administration, and a refreshing lack of intellectual property difficulties, all of which help keep costs low. This is especially important as we move closer to a time when we may be able to target prodromal and preclinical Alzheimer's disease for secondary prevention. Because secondary prevention entails treating a large

population, it would be especially beneficial if a secondary preventive intervention was also economical, which is doubtful with the currently investigated treatments (for example, passive immunotherapy and beta-secretase inhibition) (Zhao et al. 2020).

6.5.2 Polyphenols as Mitochondrial Medicine in Neurons

Wine polyphenols have been shown to lower oxidative stress and boost the production of antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase. Resveratrol increases antiapoptotic Bcl-2 protein expression while decreasing Bax protein expression. Resveratrol also acted as a mitochondrial antioxidant by increasing the levels of the antioxidants thioredoxin-2 (TRX2) and X-chromosome-linked inhibitor of apoptosis protein (Tsai et al. 2017). Another study discovered that resveratrol enhanced Bcl-2 expression, which prevented neuronal death. Resveratrol reduced mitochondria-mediated apoptosis and regulated oxidative stress in PC12 cells by downregulating Bax and upregulating Bcl-2. Similarly, lutein has been found to protect mice from ischemia damage by increasing Bcl-2 levels while decreasing Cox-2 and pancreatic ER kinase (PERK). Baicalein also inhibited mitochondrial apoptosis by reducing Bax and tBid expression and elevating Bcl-2-like proteins in the cytoplasm. Ferulic acid, a phenolic acid, inhibits mitochondrial apoptosis by inhibiting Bax and tBid expression and elevating Bcl-2-like proteins (Rodrigo et al. 2013). Flavones like chrysin, apigenin, and luteolin upregulate important ERK/Nrf2 pathway transcription factors including glutamate cysteine ligase catalytic (GCLC) and glutamate-cysteine ligase, modifier subunit (GCLM) to resist oxidative stress. The levels of glutathione peroxidase (GPx) were altered by red wine polyphenols, resulting in oxidative stress resistance. In hypoxia studies, the phenolic antioxidant 3,3′, 5,5′-tetra-t-butyl-biphenyl-4,4′-diol regulated both HIF-1α and GPx expression levels. Hesperidin carsonic acid, a key rosemary polyphenol, inhibits ROS, MAPKs, caspase-3, and COX-2 in neurons during hypoxic stress, resulting in significant anti-inflammatory effects. JNK inhibition is used as a mitochondrial treatment in not only stroke but also in Alzheimer's disease, as JNK activation contributes to tau hyperphosphorylation and A pathogenesis in the AD brain. Curcumin and resveratrol showed neuroprotection in astrocytes via increasing the activity of NAD(P)H quinone oxidoreductase (NQO1) via the Nrf2 pathway. Likewise, structurally modified isomers of resveratrol increased NQO1 activity, suggesting that antioxidant effects via the NRf2 pathway are possible. Endophilin-B1, otherwise known as SH3GLB1, which is essential for mitochondrial morphology and has a role in apoptosis, was regulated by ECG. Superoxide dismutase (SOD) and glutathione peroxidase (GPX1), two mitochondrial antioxidant enzymes, were also upregulated by EGCG (Bhullar and Rupasinghe 2013).

In a mouse model of hypoxic-ischemic (HI) brain damage, flavonoid-enriched fraction (AF4) isolates obtained from the peel of "Northern Spy" apples were shown

to suppress the expression of IL-1, TNF-, and IL-6. Phloridzin, another apple polyphenol, was shown to increase the expression of SOD1 and SOD2 genes, thus safeguarding mitochondria against oxidative stress. Polyphenols are essential mitochondrial therapies because they modulate apoptosis, antioxidant activity, signal transmission, and inflammation in mitochondrial biochemistry (Al-Gubory et al. 2010).

6.5.3 *Nanotechnology as a Novel Polyphenol Delivery Method*

The most well-studied nanoparticle-mediated polyphenol delivery techniques use biodegradable and biocompatible polymers to encapsulate polyphenolic compounds in nanostructures such as NSs, NCs, SLNs, CDs, LSs, and MCs. Oral, intravenous, intraperitoneal, and transdermal delivery are all options for delivering these nanoparticles. NSs are spherical particles with sizes ranging from 10 to 200 nm that have a hydrophobic component in the center and hydrophilic chains arranged on the surface. They protect the medication against enzymatic and chemical breakdown and might be amorphous or crystalline in form. Polyglycolic acid (PGA), polylactic acid (PLA), poly-lactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), polycaprolactone (PCL), and chitosan (CS) are the most commonly used polymers for the preparation of nanoparticles because they have homogeneous solid matrices in which the polymer chains are organized in a frozen status phase-separated from the core of the solution. The medication is essentially dissolved, entrapped, encapsulated, or chemically attached to the polymer matrix (Siddiqui et al. 2009). Nanocapsules (NCs) have a diameter of 10–1000 nm. They are made up of a core–shell construction in which the medication is put in a cavity that is encased in a polymer membrane or coating. The medication can be in liquid, solid, or molecular dispersion form in the cavity of nanocapsules. In addition, active chemicals can be transported on nanovector surfaces or ingested through the polymeric membrane.

Solid lipid nanoparticles (SLNs) are nanoparticles that range in size from 50 to 1000 nanometers. They are one of the innovative possible colloidal carrier systems made up of lipid emulsions (oil in water) with a solid core lipid covered with aqueous surfactants in place of the liquid lipid. These nanoparticles have a number of benefits, including great biocompatibility, bioavailability, physical stability, and tolerability, as well as the capacity to preserve integrated labile medicines from degradation. Another benefit of using SLNs is the relative simplicity with which large-scale manufacturing may be accomplished. Nonetheless, particle development, an unpredictable gelation propensity, and unanticipated polymeric transition dynamics are all frequent drawbacks of these nanoparticles (Faridi Esfanjani and Jafari 2016).

Cyclodextrins (CDs) are a collection of structurally similar natural compounds that are formed when cellulose is digested by bacteria. CDs are toroidal or cone-shaped rather than perfect cylinders due to the limitation of unrestricted rotation around the bonds linking the glucopyranose units. The hydroxyl functions are directed to the cone's exterior, and the center cavity is covered with the glucose residues' skeletal carbons and ethereal oxygens. Alpha, beta, and gamma CDs are natural CDs that contain six, seven, and eight glucopyranose units, respectively. There have also been reports of CDs having 9 to 13 glucopyranose units. The CDs, particularly cyclodextrin, have a low water solubility. Many other types of modified CDs have been created, but only those made using water-soluble CD derivatives have been employed commercially in the pharmaceutical industry. The hydroxypropyl (HP), methyl (M), and sulfobutylether (SBE) substituents are present in these potent CD derivatives. CDs have been employed as complexing agents to boost the bioavailability and stability of weakly water-soluble medicines by incorporating them into the CD cavity via van der Waals forces, hydrophobic interactions, or hydrogen bonds (Nonaka et al. 2008).

The most well-studied nanosized carriers for targeted drug delivery are liposomes (LSs). LSs are phospholipid vesicles with particle sizes ranging from 30 nm to several micrometers that are made up of one or more concentric lipid bilayers surrounding aqueous gaps. They self-assemble by hydrating lipid powder in an aqueous solution including cholesterols, sphingolipids, glycolipids, membrane proteins, and nontoxic surfactants. Liposomal vesicles can encapsulate a wide spectrum of medicines due to their capacity to entrap both lipophilic and hydrophilic molecules; hydrophobic molecules are imprisoned in the lipid bilayer membrane, while hydrophilic molecules can be imbedded in the aqueous gaps. The ability to self-assemble and biocompatibility are two benefits of liposomal delivery methods. Furthermore, medication molecules are protected against early inactivation, degradation, and dilution in the circulation when they are encapsulated within liposomes (Squillaro et al. 2018).

Micelles (MCs) are self-assembled, nanoscale colloidal particles with diameters ranging from 5 to 100 nm. They are made up of amphiphilic copolymers that self-assemble in aquatic environments at specific concentrations and temperatures. When the surfactant concentration exceeds the critical micelle concentration (CMC), which is defined as "the minimum surfactant concentration necessary for the self-aggregation process," MCs develop. The hydrophilic parts of the surfactants pointing outward toward the solvent create the shells, while the hydrophobic pieces of the surfactants pointing toward the micelle's center or interior constitute the core (Ghaywat et al. 2021).

The use of biodegradable and biocompatible polymers allows for a more rational design of novel nanostructures capable of encapsulating polyphenols that can cross the BBB, overcoming the limits of traditional administration methods. Curcumin is the most researched therapeutic option in this situation, owing to promising results in animal models of neurodegenerative disorders. However, curcumin's efficiency has so far been restricted by its poor water solubility, low gastrointestinal adsorption, and fast metabolism. Crossing the BBB with poly-lactic-co-glycolic acid (PLGA)

nanospheres containing curcumin may be the best method. Curcumin–PLGA nanoparticles have been shown to interfere with A aggregation and enhance the brain self-repair process, boosting neural stem cell proliferation and neuronal differentiation in recent studies. Similarly, curcumin-loaded liposomes can effectively prevent the production of Aβ fibrils in vitro and their deposition in the brain. MD and central oxidative stress appear to be helped by curcumin–solid lipid nanoparticles. Curcumin and piperine co-loaded glycerol mono-oleate nanoparticles can also inhibit Syn aggregation, decreasing oxidative stress and apoptosis. Curcumin was also considered for administration to the central nervous system using nanoemulsions intranasally. Nanoemulsions of curcumin (added in the oil phase) may efficiently traverse the mucosa in the presence of CS without causing cytotoxicity (Rafiee et al. 2019).

Resveratrol is another potential possibility. It is well-known for its propensity to cause APP degradation and the removal of A. Resveratrol, on the other hand, has a variable bioavailability due to its fast and extensive metabolism. PEG-PCL and PLGA nanoparticles containing resveratrol provide a regulated release profile of the medication, which is necessary for maintaining its plasmatic level and antioxidant action. The oil-in-water nanoemulsion is a promising technique. With the addition of Vitamin E and other surfactants, this formulation can effectively reach the brain via the nasal route. Curcumin and resveratrol (1:1 weight ratio) are also co-encapsulated in mucoadhesive nanoemulsions, which shield the active ingredients from degradation and retain their antioxidant effects. In vivo quantification of the two polyphenols in the animal brain revealed an increase in their amounts after 6 hours. Unfortunately, these systems have not yet been tested in clinical trials, but the data gathered thus far encourages the development of novel treatment methods (Ratheesh et al. 2017).

6.6 Conclusion

Despite mounting evidence of dietary polyphenols' positive benefits in the prevention and treatment of NDs and brain tumors, their limited bioavailability is a major roadblock to their widespread use in clinical practice. Clinical hurdles researchers must overcome include a lack of clinical studies based on the use of polyphenols for the treatment of NDs and brain tumors, as well as a failure to replicate in vivo the therapeutic benefits seen in in vitro models. Neurodegenerative disorders are becoming a major issue for modern society as people live longer. In fact, as the population ages, neurodegenerative diseases will have a greater influence on medical and socioeconomic circumstances in industrialized countries. As a result, it is critical to developing techniques that help persons with dementia avoid cognitive deterioration and enhance their quality of life (Bhullar and Rupasinghe 2013).

Polyphenols are bioactive chemicals found in foods and drinks that have the ability to influence the metabolic process, therefore improving health and avoiding cognitive, motor, and sensory loss as people age. They also protect cells from stress

damage by modulating several cellular signaling pathways. Understanding the molecular processes by which polyphenols work is therefore critical for using them as dietary supplements to prevent neurodegenerative diseases. Polyphenols also protect mitochondria by activating prosurvival cell signaling, which protects them against pathogenic events. Polyphenols boost antioxidant enzymes including catalase and superoxide dismutase (SOD1, SOD2), as well as prosurvival pathways like Bcl-2 and PERK. The survival of neurons is also aided by the downregulation of Bad/Bax, c-jun, JNK, COX2, AP-1, and caspase-3.

Following advancements in the synthesis and characterization of novel materials, nanotechnologies have become widely employed in everyday life. Innovative nanotechnology-based technologies for improved drug delivery and cell targeting are expected to make significant advances in the medical and pharmacology areas.

Polyphenol research in the future should strive toward the clinical acceptability of health claims derived from preclinical in vitro and animal model studies. As a result, future research should focus on human clinical trials of various strong polyphenols and their combinations. Polyphenols must also be examined for risk assessment and safety evaluation in order to detect any negative effects. Polyphenols' pharmacological importance for humans will be determined by their clinical research results (Kumar 2015).

References

Ajami M, Pazoki-Toroudi H, Amani H et al (2017) Therapeutic role of sirtuins in neurodegenerative disease and their modulation by polyphenols. Neurosci Biobehav Rev 73:39–47. https://doi.org/10.1016/j.neubiorev.2016.11.022

Al-Gubory KH, Fowler PA, Garrel C (2010) The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. Int J Biochem Cell Biol 42:1634–1650. https://doi.org/10.1016/j.biocel.2010.06.001

Ataie A, Sabetkasaei M, Haghparast A et al (2010) Curcumin exerts neuroprotective effects against homocysteine intracerebroventricular injection-induced cognitive impairment and oxidative stress in rat brain. J Med Food 13:821–826. https://doi.org/10.1089/jmf.2009.1278

Bagetta D, Maruca A, Lupia A et al (2020) Mediterranean products as promising source of multi-target agents in the treatment of metabolic syndrome. Eur J Med Chem 186:111903. https://doi.org/10.1016/j.ejmech.2019.111903

Bhullar KS, Rupasinghe HPV (2013) Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. Oxidative Med Cell Longev 2013:891748. https://doi.org/10.1155/2013/891748

Biessels GJ, Strachan MWJ, Visseren FLJ et al (2014) Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol 2:246–255. https://doi.org/10.1016/S2213-8587(13)70088-3

Dai J, Mumper RJ (2010) Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. Molecules 15:7313–7352. https://doi.org/10.3390/molecules15107313

Darvesh AS, Carroll RT, Bishayee A et al (2010) Oxidative stress and Alzheimer's disease: dietary polyphenols as potential therapeutic agents. Expert Rev Neurother 10:729–745. https://doi.org/10.1586/ern.10.42

Darvesh AS, McClure M, Sadana P et al (2017) Neuroprotective properties of dietary polyphenols in Parkinson's disease. In: Farooqui T, Farooqui AA (eds) Neuroprotective effects of phytochemicals in neurological disorders. John Wiley & Sons, Inc., Hoboken, NJ, pp 243–263

Das S, Das DK (2007) Anti-inflammatory responses of resveratrol. Inflamm Allergy Drug Targets 6:168–173. https://doi.org/10.2174/187152807781696464

Faridi Esfanjani A, Jafari SM (2016) Biopolymer nano-particles and natural nano-carriers for nano-encapsulation of phenolic compounds. Colloids Surf B Biointerfaces 146:532–543. https://doi.org/10.1016/j.colsurfb.2016.06.053

Farzaei MH, El-Senduny FF, Momtaz S et al (2018) An update on dietary consideration in inflammatory bowel disease: anthocyanins and more. Expert Rev Gastroenterol Hepatol 12:1007–1024. https://doi.org/10.1080/17474124.2018.1513322

Francis FJ (1982) Analysis of anthocyanins. In: Anthocyanins as food colors. Elsevier, pp 181–207

Ghaywat SD, Mate PS, Parsutkar YM et al (2021) Overview of nanogel and its applications. GSC Biol Pharm Sci 16:040–061. https://doi.org/10.30574/gscbps.2021.16.1.0196

Ghosh R, Tabrizi SJ (2018) Clinical features of Huntington's disease. Adv Exp Med Biol 1049:1–28. https://doi.org/10.1007/978-3-319-71779-1_1

Gottlieb M, Leal-Campanario R, Campos-Esparza MR et al (2006) Neuroprotection by two polyphenols following excitotoxicity and experimental ischemia. Neurobiol Dis 23:374–386. https://doi.org/10.1016/j.nbd.2006.03.017

Halliday GM, McCann H (2010) The progression of pathology in Parkinson's disease. Ann N Y Acad Sci 1184:188–195. https://doi.org/10.1111/j.1749-6632.2009.05118.x

Han X, Shen T, Lou H (2007) Dietary polyphenols and their biological significance. IJMS 8:950–988. https://doi.org/10.3390/i8090950

Hano C, Tungmunnithum D (2020) Plant polyphenols, more than just simple natural antioxidants: oxidative stress, aging and age-related diseases. Medicines (Basel) 7:26. https://doi.org/10.3390/medicines7050026

Holley SM, Kamdjou T, Reidling JC et al (2018) Therapeutic effects of stem cells in rodent models of Huntington's disease: review and electrophysiological findings. CNS Neurosci Ther 24:329–342. https://doi.org/10.1111/cns.12839

Inanami O, Asanuma T, Inukai N et al (1995) The suppression of age-related accumulation of lipid peroxides in rat brain by administration of rooibos tea (*Aspalathus linearis*). Neurosci Lett 196:85–88. https://doi.org/10.1016/0304-3940(95)11853-o

Ingale SP, Kasture SB (2014) Antioxidant and antiparkinsonian activity of Passiflora incarnata leaves. Orient Pharm Exp Med 14:231–236. https://doi.org/10.1007/s13596-014-0149-3

Ishrat T, Parveen K, Khan MM et al (2009) Selenium prevents cognitive decline and oxidative damage in rat model of streptozotocin-induced experimental dementia of Alzheimer's type. Brain Res 1281:117–127. https://doi.org/10.1016/j.brainres.2009.04.010

Kamat CD, Gadal S, Mhatre M et al (2008) Antioxidants in central nervous system diseases: preclinical promise and translational challenges. J Alzheimers Dis 15:473–493

Kang GG, Francis N, Hill R et al (2019) Dietary polyphenols and gene expression in molecular pathways associated with type 2 diabetes mellitus: a review. Int J Mol Sci 21(1):140. https://doi.org/10.3390/ijms21010140

Kelsey NA, Wilkins HM, Linseman DA (2010) Nutraceutical antioxidants as novel neuroprotective agents. Molecules 15:7792–7814. https://doi.org/10.3390/molecules15117792

Klatt P, Lamas S (2000) Regulation of protein function by S-glutathiolation in response to oxidative and nitrosative stress. Eur J Biochem 267:4928–4944. https://doi.org/10.1046/j.1432-1327.2000.01601.x

Korkina L, Kostyuk V, De Luca C, Pastore S (2011) Plant phenylpropanoids as emerging anti-inflammatory agents. Mini Rev Med Chem 11:823–835

Kumar R (2015) Development and elucidation of mechanism of action of new leads to attenuate NEUROINFLAMMATION in stroke model. Undergraduate thesis

Lassmann H (2018) Multiple sclerosis pathology. Cold Spring Harb Perspect Med 8(3):a028936. https://doi.org/10.1101/cshperspect.a028936

Lassmann H, van Horssen J, Mahad D (2012) Progressive multiple sclerosis: pathology and pathogenesis. Nat Rev Neurol 8:647–656. https://doi.org/10.1038/nrneurol.2012.168

Lissek V, Suchan B (2021) Preventing dementia? Interventional approaches in mild cognitive impairment. Neurosci Biobehav Rev 122:143–164. https://doi.org/10.1016/j.neubiorev.2020.12.022

Matkowski A, Kus P, Goralska E, Wozniak D (2013) Mangiferin–a bioactive xanthonoid, not only from mango and not just antioxidant. Mini Rev Med Chem 13:439–455

McKay DL, Blumberg JB (2007) A review of the bioactivity of south African herbal teas: rooibos (*Aspalathus linearis*) and honeybush (*Cyclopia intermedia*). Phytother Res 21:1–16. https://doi.org/10.1002/ptr.1992

Milatovic D, Gupta RC, Zaja-Milatovic S, Aschner M (2009) Excitotoxicity, oxidative stress, and neuronal injury. In: Handbook of toxicology of chemical warfare agents. Elsevier, pp 633–651

Nonaka N, Farr SA, Kageyama H et al (2008) Delivery of galanin-like peptide to the brain: targeting with intranasal delivery and cyclodextrins. J Pharmacol Exp Ther 325:513–519. https://doi.org/10.1124/jpet.107.132381

Oliviero F, Scanu A, Zamudio-Cuevas Y et al (2018) Anti-inflammatory effects of polyphenols in arthritis. J Sci Food Agric 98:1653–1659. https://doi.org/10.1002/jsfa.8664

Przedborski S, Vila M, Jackson-Lewis V (2003) Series introduction: neurodegeneration: what is it and where are we? J Clin Invest 111:3–10. https://doi.org/10.1172/JCI200317522

Rafiee Z, Nejatian M, Daeihamed M, Jafari SM (2019) Application of different nanocarriers for encapsulation of curcumin. Crit Rev Food Sci Nutr 59:3468–3497. https://doi.org/10.1080/10408398.2018.1495174

Rahimifard M, Maqbool F, Moeini-Nodeh S et al (2017) Targeting the TLR4 signaling pathway by polyphenols: a novel therapeutic strategy for neuroinflammation. Ageing Res Rev 36:11–19. https://doi.org/10.1016/j.arr.2017.02.004

Ratheesh G, Tian L, Venugopal JR et al (2017) Role of medicinal plants in neurodegenerative diseases. Biomanuf Rev 2:2. https://doi.org/10.1007/s40898-017-0004-7

Rehman IU, Ahmad R, Khan I et al (2021) Nicotinamide ameliorates amyloid beta-induced oxidative stress-mediated neuroinflammation and neurodegeneration in adult mouse brain. Biomedicines 9(4):408. https://doi.org/10.3390/biomedicines9040408

Rodrigo R, Fernández-Gajardo R, Gutiérrez R et al (2013) Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. CNS Neurol Disord Drug Targets 12:698–714. https://doi.org/10.2174/18715273113120500015

Scalbert A, Johnson IT, Saltmarsh M (2005) Polyphenols: antioxidants and beyond. Am J Clin Nutr 81:215S–217S. https://doi.org/10.1093/ajcn/81.1.215S

Selkoe DJ (1991) The molecular pathology of Alzheimer's disease. Neuron 6:487–498. https://doi.org/10.1016/0896-6273(91)90052-2

Sharma RA, Gescher AJ, Steward WP (2005) Curcumin: the story so far. Eur J Cancer 41:1955–1968. https://doi.org/10.1016/j.ejca.2005.05.009

Shoval H, Weiner L, Gazit E et al (2008) Polyphenol-induced dissociation of various amyloid fibrils results in a methionine-independent formation of ROS. Biochim Biophys Acta 1784:1570–1577. https://doi.org/10.1016/j.bbapap.2008.08.007

Siddiqui IA, Adhami VM, Bharali DJ et al (2009) Introducing nanochemoprevention as a novel approach for cancer control: proof of principle with green tea polyphenol epigallocatechin-3-gallate. Cancer Res 69:1712–1716. https://doi.org/10.1158/0008-5472.CAN-08-3978

Snijman PW, Joubert E, Ferreira D et al (2009) Antioxidant activity of the dihydrochalcones Aspalathin and Nothofagin and their corresponding flavones in relation to other rooibos (*Aspalathus linearis*) flavonoids, epigallocatechin Gallate, and Trolox. J Agric Food Chem 57:6678–6684. https://doi.org/10.1021/jf901417k

Squillaro T, Cimini A, Peluso G et al (2018) Nano-delivery systems for encapsulation of dietary polyphenols: an experimental approach for neurodegenerative diseases and brain tumors. Biochem Pharmacol 154:303–317. https://doi.org/10.1016/j.bcp.2018.05.016

Stadelmann C (2011) Multiple sclerosis as a neurodegenerative disease: pathology, mechanisms and therapeutic implications. Curr Opin Neurol 24:224–229. https://doi.org/10.1097/WCO.0b013e328346056f

Street RA, Prinsloo G (2013) Commercially important medicinal plants of South Africa: a review. J Chem 2013:1–16. https://doi.org/10.1155/2013/205048

Stutzmann GE (2007) The pathogenesis of Alzheimers disease is it a lifelong "calciumopathy"? Neuroscientist 13:546–559. https://doi.org/10.1177/1073858407299730

Taylor AE, Saintcyr JA (1995) The neuropsychology of Parkinsons-disease. Brain Cogn 28:281–296. https://doi.org/10.1006/brcg.1995.1258

Tian B, Liu J (2020) Resveratrol: a review of plant sources, synthesis, stability, modification and food application. J Sci Food Agric 100:1392–1404. https://doi.org/10.1002/jsfa.10152

Tønnesen HH, Karlsen J (1985) Studies on curcumin and curcuminoids. VI. Kinetics of curcumin degradation in aqueous solution. Z Lebensm Unters Forsch 180:402–404. https://doi.org/10.1007/BF01027775

Tsai H-Y, Ho C-T, Chen Y-K (2017) Biological actions and molecular effects of resveratrol, pterostilbene, and 3′-hydroxypterostilbene. J Food Drug Anal 25:134–147. https://doi.org/10.1016/j.jfda.2016.07.004

Tsuji S (2002) Contribution of Japanese researchers to progress in the field of neurology in the last 100 years: Dentatorubral-pallidoluysian atrophy. Nippon Naika Gakkai Zasshi 91:2296–2301

Tuñón MJ, García-Mediavilla MV, Sánchez-Campos S, González-Gallego J (2009) Potential of flavonoids as anti-inflammatory agents: modulation of pro-inflammatory gene expression and signal transduction pathways. Curr Drug Metab 10:256–271. https://doi.org/10.2174/138920009787846369

Udhayakumar B (2020) Myloid beta (Aβ) aggregates and/or fibril development... - Google Scholar. Brain Amyloidopathy in a Mouse Model of Alzheimer's Pathology

Valls V, Peiro C, Muñiz P, Saez GT (2005) Age-related changes in antioxidant status and oxidative damage to lipids and dna in mitochondria of rat liver. Process Biochem 40:903–908. https://doi.org/10.1016/j.procbio.2004.02.025

van der Burg JMM, Björkqvist M, Brundin P (2009) Beyond the brain: widespread pathology in Huntington's disease. Lancet Neurol 8:765–774. https://doi.org/10.1016/S1474-4422(09)70178-4

Vonsattel JP, DiFiglia M (1998) Huntington disease. J Neuropathol Exp Neurol 57:369–384. https://doi.org/10.1097/00005072-199805000-00001

Williams RJ, Spencer JPE, Rice-Evans C (2004) Flavonoids: antioxidants or signalling molecules? Free Radic Biol Med 36:838–849. https://doi.org/10.1016/j.freeradbiomed.2004.01.001

Xing L, Zhang H, Qi R et al (2019) Recent advances in the understanding of the health benefits and molecular mechanisms associated with green tea polyphenols. J Agric Food Chem 67:1029–1043. https://doi.org/10.1021/acs.jafc.8b06146

Xu Q, Chen Z, Zhu B et al (2020) A-type cinnamon Procyanidin oligomers protect against 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-induced neurotoxicity in mice through inhibiting the P38 mitogen-activated protein kinase/P53/BCL-2 associated X protein signaling pathway. J Nutr 150:1731–1737. https://doi.org/10.1093/jn/nxaa128

Youdim BH, Mandel S (2012) Orly Weinreb, Tamar Amit, Moussa. In: Flavonoids and related compounds: bioavailability and function

Zhao D, Simon JE, Wu Q (2020) A critical review on grape polyphenols for neuroprotection: strategies to enhance bioefficacy. Crit Rev Food Sci Nutr 60:597–625. https://doi.org/10.1080/10408398.2018.1546668