Chapter 8
Role of Endogenous and Dietary Antioxidants in Brain Disorders

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8.1 Introduction

Oxidative stress (OS) occurs as a result of the disturbance in the production of prooxidant and antioxidant species. It can be brought by a decline of antioxidant species and an increase in oxidative metabolism that can occur due to many other factors, such as drinking alcohol, being exposed to the cold, taking medications, being injured, ingesting toxins, being exposed to radiation, engaging in strenuous exercise, and eating poorly. In addition to harming lipids, reactive oxygen species

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(ROS) can also result in cell death. They are produced during regular cellular processes like arachidonic acid metabolism, phagocytic digestion, mitochondrial respiration, ovulation, and fertilization. When there are pathological situations, however, their production multiplies many times. Hydrogen peroxide, Superoxide ions, peroxynitrite, and nitric oxide play a part in tissue destruction in pathological conditions.

8.1.1 Oxidative Stress and the Nervous System

The Central Nervous System (CNS) is particularly prone to oxidative injury for some reasons:

1. The extremely active oxidative metabolism of brain tissue results in high amounts of intra-cellular superoxides.
2. It has a limited capacity for anaerobic respiration, which results in elevated superoxide levels in anoxic environments.
3. High iron concentration, decrement of antioxidant species, and membrane elaborations in cellular characteristics make the oligodendrocyte population more susceptible to oxidative damage.
4. Myelin is a preferred target for ROS because of its high protein/lipid ratio. Due to their high mitochondrial density and increased rate of oxygen utilization, CNS tissues are particularly susceptible to OS. As a result of their regular oxidative metabolism, mitochondria invariably produce free radicals, that can harm the DNA of mitochondria. It leads to the production of defective proteins that reduces the generation of mitochondrial elements of the electron-transport chain, which can then increase free radical generation and further mitochondrial damage.

Additionally, CNS is abundant in iron and unsaturated fatty acids. Neural tissue is especially susceptible to oxidative injury due to high aerobic metabolic activity and lipid content. Iron is a crucial component for the development of the brain, yet brain cell damage can release iron ions that cause OS by catalyzing the production of ROS. The production of free radicals can cause serious damage to particular catecholamine-rich brain regions. Endogenous, as well as dietary antioxidants (Fig. 8.1), can shield the nervous system from harm brought on by OS, which is a contributing factor in the development of brain disorders [1–4].

8.1.2 Antioxidants and the Nervous System

Antioxidants are those species that remove free radicals, scavenge ROS or their precursors, and prevent ROS synthesis. Neurons are especially susceptible to damage brought on by OS because of their reduced antioxidant defense system, high

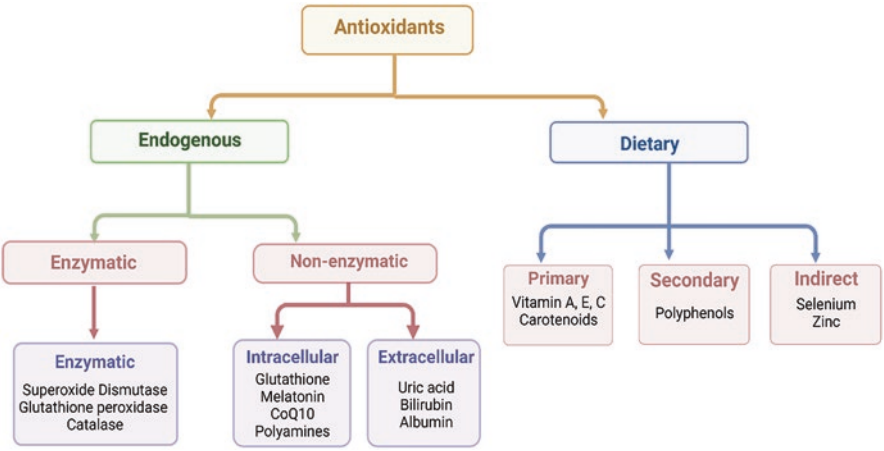

Fig. 8.1 Classification of endogenous and dietary antioxidants

need for oxygen utilization, and high contents of polyunsaturated fatty acids (PUFAs) in their cell membranes [5]. By quenching/scavenging free radical intermediates and halting the spread of oxidative chain events, antioxidants can alleviate OS. These antioxidants are mostly made up of exogenous (natural and synthetic) antioxidant sources that keep the biological system's redox balance in check as well as a variety of endogenous antioxidant enzymes and their coenzymes or substrates [6, 7].

All cells, including neurons, contain potent antioxidant enzymes that can assist detoxify ROS. Catalases, superoxide dismutases (SOD), and glutathione peroxidases (GPx) are the three main types of antioxidant enzymes. These antioxidant enzymes prevent cellular damage brought on by ROS. The antioxidant defense mechanisms in the brain itself, however, seem to be somewhat underwhelming. The majority of brain areas, except the substantia nigra and the hypothalamus, have relatively low amounts of catalase. Additionally, any catalase that is present is housed in micro peroxisomes, where it is unable to reduce the H_2O_2 generated in other subcellular spaces. Therefore, it appears that the brain's endogenous antioxidant defense system is easily overpowered if ROS generation rises too quickly. External antioxidant supplementation or herbal treatments may help maintain strict homeostatic regulation of ROS and prevent OS. A growing body of research indicates that consuming antioxidants including vitamin E, ascorbate, carotenoids, and plant phenols may lower the risk of some neurodegenerative illnesses. These antioxidants can be consumed naturally or as supplements [8, 9]. The neuroprotective effects of dietary and endogenous antioxidants in brain disorders have been discussed in detail in the next sections of this chapter:

8.2 Antioxidants and Parkinson's Disease

Parkinson's Disease (PD) is characterized by the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Rigidity, tremor, bradykinesia, bradyphrenia, gait impairment, and postural instability are the main effects. Dopaminergic neurons in the SN provide signals to the adult hippocampus dentate gyrus (DG). Therefore, the decline of dopaminergic neurons could have a direct impact on adult hippocampus neurogenesis. Lewy bodies (LB) are linked to the pathophysiology of PD, and the main LB component that aggregates in PD is α-synuclein [10, 11]. Mitochondrial malfunction and OS are key factors in the development of the illness. Oxidative phosphorylation, which takes place at the mitochondrial level and is a by-product of aerobic respiration and produces ROS. Because of their high energy requirements and huge oxygen consumption as well as their post-mitotic origin, neurons are thought to be particularly vulnerable to ROS-induced injury. That's why neural tissues are susceptible to long-term and degenerative illnesses, such as PD [12].

8.2.1 Endogenous Antioxidants

8.2.1.1 Glutathione

Reduced Glutathione (GSH) levels and a lower GSH/GSSG ratio in the blood, lymphoblastoid cells and brain tissues have been seen in PD patients. The cerebellum and temporal cortex of people with PD have significantly lower GSH total contents and GSH/GSSG ratios. Patients with PD exhibit higher levels of circulating Hcy and lower levels of cellular GSH as a result of elevated OS and impaired methionine synthase activity. The brains of PD patients also show more chronic inflammatory responses, mitochondrial superoxide, as well as oxidative damage to proteins and DNA, due to the increased OS and decreased GSH/GSSG activity [13, 14]. Mice given glut amyl cysteine ethyl ester, dipeptide precursor of GSH, in a lipid-soluble form can cross the blood-brain barrier (BBB) and showed some resistance to the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced loss of dopaminergic neurons [15].

8.2.1.2 Coenzyme Q10

Coenzyme Q10 (CoQ10) is ubiquinone that is found in almost all cells and is a vital part of the oxidative phosphorylation process in the mitochondria. In contrast to healthy persons, postmortem brain tissues from people with PD showed significantly lower levels of total plasma CoQ10 as well as significantly higher amounts of the oxidized form of ubiquinone. More particular, PD patients' platelets had lower

levels of mitochondrial CoQ10 than controls of similar ages and sexes. In vitro PD models have shown the potency of CoQ10 as protection against cell toxicity. When adult mice's striatal slices were grown and treated with MPP+, the co-incubation with CoQ10 resulted in a dramatically reduced loss of dopaminergic cells. In vitro PD models have shown the potency of CoQ10 as protection against cell toxicity [16]. A decline in CoQ10 status contributes to the pathogenesis of the disease by aggravating MRC function and impairing cellular antioxidants [17].

8.2.1.3 Uric Acid

Uric acid (UA) shields dopaminergic neurons against H_2O_2 or MPP+ induced apoptosis in cultured SN neurons from mice. In 6 hydroxydopamine (6-OHDA) lesioned rats, elevated cerebral uric acid improves parkinsonian phenotypes. Higher serum UA concentration is strongly linked with a slower rate of PD progression. In contrast to those without cognitive impairment, PD patients with cognitive defects also have lower serum uric acid levels [18].

8.2.1.4 Alpha Lipoic Acid

Alpha Lipoic Acid (ALA) has potential therapeutic utility since it has anti-inflammatory, anti-oxidative, and free radical formation-inhibiting properties. It can lessen dyskinesia by increasing GSH activity and decreasing malondialdehyde (MDA), a byproduct of lipid peroxidation. ALA treatment significantly improves motor dysfunctions, causes a decrease in α-synuclein accumulation, and a reduction in the activation of pro-inflammatory molecules [19].

8.2.2 Dietary Antioxidants

8.2.2.1 Vitamin C

Vitamin C, also known as ascorbate or ascorbic acid can be obtained from fruits and vegetables (Fig. 8.2). The majority of mammals can produce vitamin C internally, but because humans lack the enzyme L-gulonolactone oxidase, they must consume this vital component through diet or supplements. By giving electrons to counteract the harmful effects of free radicals, vitamin C functions as an antioxidant. Vitamin C increased antioxidant enzyme activity and reduced the PD-related phenotype by reducing the antioxidant enzyme ubiquitin c-terminal hydrolase (UCH), which increases the age-related deterioration of dopaminergic neurons and lowers dopamine levels in the brain [20].

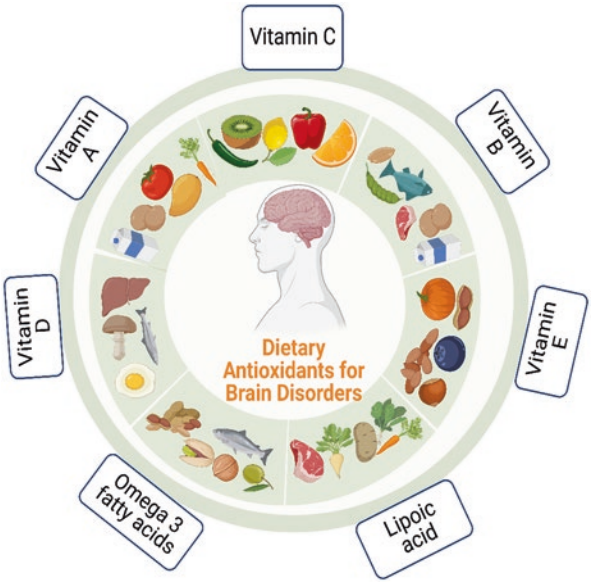

Fig. 8.2 Sources of dietary antioxidants for brain disorders

8.2.2.2 Vitamin E

Microtubule-associated protein tau (MAPT) gene polymorphisms are associated with an increased risk of PD, and MAPT methylation is linked negatively to MAPT expression. Vitamin E reduces the incidence of PD by reducing MAPT expression through raising MAPT gene methylation. Vitamin E administration is found to prevent PD and ameliorate its prognosis [21].

8.2.2.3 Phenols

Curcumin is found to enhance locomotion, lessen severe neurodegeneration, and lower OS markers in both 6-OHDA-induced PD in rats and *Drosophila milanogaster* models. Curcumin protects SN neurons by increasing dopamine levels in the nigrostriatal tract and lowering Fe^{3+} levels via chelation in the 6-OHDA rat model of PD. This is because the phenolic rings and diketone groups on the curcumin moiety function as an electron trap, reducing the production of superoxide, H_2O_2, and hydroxyl ions. It reduces ROS production and NF-κB overexpression and increases SOD expression to prevent 6-OHDA-actuated cell damage [22].

Resveratrol (RV) reduces astroglial activation in mice exposed to MPTP's nigrostriatal pathway. It shows synergistic effects when administered along with the dopamine precursor L-DOPA, hence, it reduces its harmful effects in the treatment of PD [23].

Tyrosol, found in extra-virgin oil, has been shown to slow down the aggregation of α-synuclein in PD. It decreases ROS levels while enhancing the expression of antioxidant enzymes and particular chaperones.

Chrysin, a naturally occurring flavonoid, is found in honey, bee propolis, and various plants. It reverses neurochemical impairments, behavioral abnormalities, and OS in 6-OHDA and MPTP-induced PD model.

Acteoside, a flavonoid, is known to lessen or even stop brain damage against the 6-OHDA zebrafish model of PD. Acteoside pretreatment may also increase the expression of antioxidants by triggering the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway.

Pinostrobin was also employed in the MPTP zebra fish model of PD with positive outcomes because it greatly increases Nrf2 expression and upregulates the expression of heme oxygenase-1 (HO-1).

Genistein activates estrogen receptors as well as NF-E2L2 channels and reduces OS damage and cell death in human SH-SY5Y cells, which reveals a mutant type of α-synuclein.

Salidroside was given to 6-OHDA-induced PD rats, and the results showed that it protected the brain from OS. This effect was most likely caused by the control of the Wnt/β-catenin signaling pathway [24].

Oleuropein (OL) reduces the harmful effects of α-synuclein-induced stress on dopaminergic neurons to treat and prevent PD. The toxicity is reduced by OL and other structurally related chemicals such as verbascoside, dihydro Oleuropein, 3-hydroxytyrosol, oleanolic acid, oleuropein glycosides, and rutin. This is accomplished by converting α-synuclein oligomers into small monomers that have less harmful effects. Moreover, OLA binds with α-synuclein's N-terminal region, preventing it from reacting with lipid membranes and preventing the creation of toxic aggressiveness. Additionally, OL protects against microglial inflammation-mediated dopaminergic neurons by reducing the pro-inflammatory action of activated microglia cells by blocking mitochondrial fission. A substantial reduction in OS, apoptosis, and cell damage was observed in adrenal pheochromocytoma (PC12) cells and 6-OHDA induced PD when different formulations of OL were supplemented into the diet. Additionally, OL lowers the levels of DNA denaturation, mitochondrial ROS generation, and superoxide anion [25].

Carvacrol promotes significant neuroprotection in the 6-OHDA model of PD via its general blocking impact upon TRPM7 cation channels, that are involved in causing neurodegeneration [26].

8.2.2.4 Asiatic Acid

Asiatic acid (AA) inhibits OS, preserves the MMP, and controls the expression of Bcl-2, Bax, and caspases to prevent rotenone-induced apoptosis in SH-SY5Y cells as well as prevented the MPP+ induced apoptosis of dopaminergic neurons.

Additionally, AA provides neuroprotection against MPP+-induced loss of neuronal cells by activating the ERK and PI3K/Akt/mTOR/GSK-3β pathways [27].

8.3 Antioxidants and Huntington's Disease

Huntington's disease (HD) occurs due to expanded polyglutamine (poly Q) in the huntingtin (Htt) protein that leads to the death of striatal neurons and eventually damages cortical regions [28]. mHtt increases OS by attaching to PGC1α's promoter region and lowers the transcriptional level of PGC1α. It also inhibits the production of antioxidant enzymes and mitochondrial uncoupling proteins by directly inactivating PGC1α. By interfering with Drp1's functionality, mHtt upsets the equilibrium between the fission-fusion process in the mitochondria. The mitochondrial permeability transition pore (mPTP) opens as a result of mHtt's induction of calcium ion leakage through the calcium channel ryanodine receptors, which also causes mitochondrial OS. Due to the downregulation of ROS defense genes like SOD1, SOD2, and GPx, oxidative damage and neuronal death are enhanced in HD [29].

Nrf2 maintains the expression of numerous antioxidant enzymes, phase I and phase II enzymes, and a number of mediators that reduce inflammation. To protect neurons and glial cells from OS, neuroinflammation, and other pathogenic insults, Nrf2 serves as a crucial defensive mechanism in HD [30–33].

8.3.1 Endogenous Antioxidants

8.3.1.1 Dichloroacetate

Dichloroacetate (DCA) is found to boost pyruvate dehydrogenase complex (PDHC) activity and reduces lactate levels in the brain. It dramatically extended survival in the R6/2 and N171-82Q transgenic mice models of HD, enhanced motor performance, postponed weight loss, reduced the onset of striatal neuron atrophy, and shielded against diabetes [33].

8.3.1.2 L-Carnitine

It plays a part in facilitating the transport of fatty acids into mitochondria and also shields cells from oxidative damage. It decreases both the loss of neurons and the number of intranuclear aggregates in neurons and exerts neuroprotective effects against HD [34].

8.3.1.3 Melatonin

Melatonin lowers lipid peroxidation levels as well as protein carbonyl content and boosts succinate dehydrogenase and SOD activity against 3-NP-induced OS in an animal model of HD. It increases neuronal survival and decreases DNA damage, reducing the rise in SOD activity, protein carbonyls, and lipid peroxidation within the striatum against the 3-NP model of HD [35].

8.3.1.4 Glutathione, Catalase, and Superoxide Dismutase

Mutant cells (GRed) displayed elevated glutathione levels in the intracellular space, as well as elevated glutathione reductase and GPx activities [36]. The striatum regions of the brains of HD patients have been detected with OS and significant activation of antioxidative stress enzymes [37, 38].

8.3.2 Dietary Antioxidants

8.3.2.1 Vitamin C

Vitamin C reverses neurodegeneration and reduces the behavioral phenotype of HD [35]. Preclinical research suggests that HD is linked to ascorbic acid insufficiency and inhibits cortical afferents' ability to release glutamate (Fig. 8.3). Moreover, sodium ascorbate has been found to restore the level of striatal extracellular ascorbate in R6/2 mice [39].

8.3.2.2 Phenols

Polyphenol such as green tea is linked to a reduction in early HD pathogenesis events, including Huntington's misfolding. The combination of fish oil and quercetin has also been said to provide defense against HD brought on by 3-nitropropionic acid [40]. Grape seed polyphenolic extract (GSPE) therapy greatly reduces polyQ aggregation in the PC12 cells and decreases motor impairments in the R6/2 mice as well as improves lifespan in both the fly and R6/2 mouse models of HD [41].

Flavonoids like hesperidin, quercetin, naringin, and EGCG in various concentrations are efficient components in both the prevention as well as treatment of HD. Flavonoids focus on a variety of pathways.

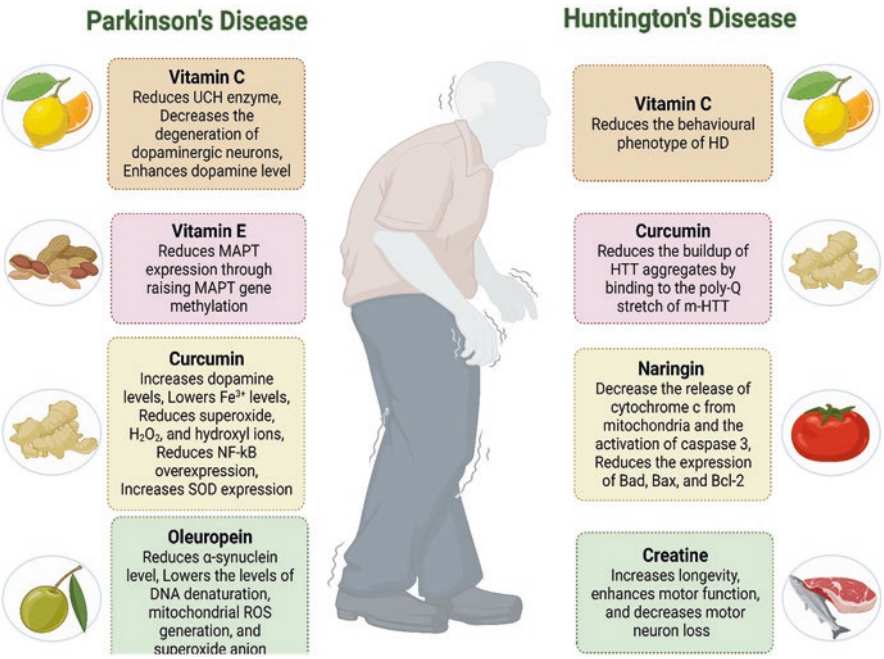

Fig. 8.3 Mechanism of Action of dietary antioxidants in Parkinson's and Huntington's disease (*UCH*: Ubiquitin C-terminal hydrolase; *MAPT*: Microtubule Associated Protein Tau; H_2O_2: Hydrogen peroxide; *NFκB*: Nuclear factor kappa B; *SOD*: Superoxide dismutase; *DNA*: Deoxyribonucleic acid; *ROS*: Reactive oxygen species; *HD*: Huntington's disease; *HTT*: Huntingtin protein; *Bad/Bax/Bcl-2*: apoptosis markers)

1. They can reduce the generation of ROS and boost the generation of glutathione, which reduces OS.
2. They can chelate metal ions and lessen metal ion toxicity which increases OS in neural tissues.

Both of these methods aid in reducing OS, which in turn causes the downregulation of inflammatory mediators and, as a result, a decrease in neuroinflammation and neuroprotection [42].

A flavonoid called **myricetin** works as the key player in an interaction with the CAG motif that stops the translation of mutant huntingtin protein and the sequestration of MBNL1. Additionally, myricetin was discovered to lessen the proteo-toxicity caused by the aggregation of polyglutamine, and its supplementation also helped to improve the HD mice model's neurobehavioral impairments [43]. **Naringin** is found to decrease the 3-NP-induced apoptosis by lowering the activation of caspase 3 and the release of cytochrome c from mitochondria. The use of Naringin also reduced the expression of Bad and Bax, two pro-apoptotic indicators. It also prevented the 3-NP-induced reduction in Bcl-2 mRNA expression [44, 45].

Curcumin at dosages of 0.01 μM in human bone marrow neuroblast cells, modulates HSP70 and HSP90 expression, reducing the buildup of HTT aggregates in HD [46]. Curcumin stimulated-HSP70 inhibits the formation of aggregates by binding to the poly-Q stretch of m-HTT, which is the mechanism behind its anti-amyloidogenic effect. Curiously, curcumin does not affect HSP90's activity on Akt, which lowers the apoptotic stimuli [47].

8.3.2.3 Creatine

It improves motor function, prolongs survival, attenuates brain and body weight loss, and lessens neuronal atrophy in N171-82Q and both R6/2 mouse models of HD, as well as the size of striatal lesions and behavioral changes brought on by neurotoxins (malonate and 3-NP). It also reduces the elevated 8-OHdG levels in the blood as well as the brain's ATP [48]. In addition, creatine treatment increases longevity, enhances motor function, and decreases motor neuron loss in N-171-82Q HD and R6/2 mice models [49].

8.4 Antioxidants and Alzheimer's Disease

Alzheimer's disease (AD) impairs memory abilities and the ability to do even the most common tasks [50, 51]. It occurs due to the buildup of β amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau [52–54]. Several oxidative damage markers have been linked to AD, including nitration, advanced glycation end products, lipid peroxidation adduction products, free carbonyls, and carbonyl-modified neurofilament protein. In AD patients, the plasma levels of antioxidants like uric acid, bilirubin, albumin, lycopene, vitamin E, vitamin C, and A were lowered [55]. It was also discovered that various AD brain regions, particularly the frontal and temporal cortices, exhibit significantly reduced activity of antioxidant enzymes like glutathione peroxidase, catalase, heme oxygenase, and superoxide dismutase [56].

8.4.1 Endogenous Antioxidants

8.4.1.1 Glutathione

Glutathione functions by causing a reduction of the protein's sulfenic ion through covalent adduction and maintains the balance of protein sulfhydryl molecules in eukaryotic cells [57]. The reduction of free radicals in mitochondria is accomplished by N-acetyl-l-cysteine choline ester and glutathione choline ester, which are produced due to the formation of the ester link between GSH and choline. It was shown

to efficiently reduce protein oxidation and prevent DNA breakage caused by the Aβ peptide in the mitochondria of AD cells or neurons damaged by mutant APP (amyloid precursor protein) [58]. Reduced GSH antioxidant activity leads to initiate the progression of AD [59].

8.4.1.2 Superoxide Dismutase

Superoxide dismutase (SOD), an enzyme, catalyzes the conversion of superoxide radicals into H_2O_2. Three separate forms of SOD are present in the body: manganese-SOD, copper/zinc-SOD (mainly in the mitochondria and cytoplasm), and extracellular SOD. Its expression and activity in the hippocampus region of the brain are decreased in AD [60]. This antioxidant is thought to play a crucial role in human aging and AD. It was seen that SOD knockout mice show an increase in tau phosphorylation, and deposition of Aβ plaques and aggravate behavioral impairments [61]. In 3X-Tg-AD, an aggressive AD mouse model, antioxidant treatment such as EUK-207, SOD mimetic, diminished the spread of tau phosphorylation and thereby reduced clinical symptoms [62].

8.4.1.3 Catalase

The peroxisomes contain the enzyme catalase, which converts approximately 6 million molecules of H_2O_2 into O_2 and H_2O per minute. Reduced catalase activity is seen in rats with AD caused by Streptozotocin (STZ) [63]. The Aβ in AD inhibits the enzyme catalase, causing H_2O_2 to build up in the hippocampal neurons [64]. It is possible for Aβ to directly or indirectly inhibit the catalase activity and encourages OS [65].

8.4.1.4 Methionine Sulfoxide Reductase

Methionine sulfoxide reductase-A (MsrA) is in charge of turning methionine sulfoxide into methionine and its expression is reduced in various areas of the brain in AD. Decreased MsrA activity alters the solubility characteristics of Aβ in AD and results in mitochondrial dysfunction; hence, increasing MsrA activity can help slow the progression of AD [66, 67].

8.4.1.5 Uric Acid

It is one of the most significant antioxidants in human bodily fluids and has antioxidant, anti-inflammatory, and neuroprotective properties. AD patients have much lower levels of UA than healthy individuals [68]. By quenching superoxide and

singlet oxygen, UA can scavenge up to 60% of free radicals in the peripheral system [69].

8.4.2 Dietary Antioxidants

8.4.2.1 Vitamin E

A well-known antioxidant called vitamin E has been shown to provide neuroprotection in AD [70]. The best sources of vitamin E include sunflower seeds, almonds, wheat germ oil, and hazelnuts [71]. Vitamin E's capacity as an antioxidant is a result of the hydroxyl group's presence in the phenolic ring structure. According to a recent meta-analysis, it has the strongest protective effects against AD [72].

8.4.2.2 Vitamin B

Vitamin B plays a protective role against AD by altering the level of phosphorylated tau, and OS, modifying the brain energy metabolism and improving cognitive function [73]. Supplementing with B vitamins is said to lessen the risk of AD with elevated homocysteine (Hcy) levels [74]. Vitamins B6, B9, and B12 cause a reduction in Hcy levels, and aid in the management of this modifiable risk factor for AD [75].

8.4.2.3 Vitamin A

Vitamin A (retinol, retinal, and retinoic acid) suppresses the synthesis, extension, and destabilizing effects of β-amyloid fibrils. It prevents the oligomerization of Aβ, reduced Aβ accumulation and tau phosphorylation, slowed neuronal degeneration, and enhanced spatial learning and memory [76, 77].

8.4.2.4 Phenols

Natural anti-oxidants called polyphenols have anti-AD effects via a variety of biological processes, including interactions with transition metals, suppression of the inflammatory response, blockage of free radicals, and modification of enzymes' activity [78]. They lower Hcy in AD patients seen in a clinical trial [79–81].

β-carotene belongs to the group of hydrocarbons called carotenoids and acts as an antioxidant. It can help with memory improvement in AD patients [82]. The diagnosis of AD was correlated with plasma β-carotene levels. Lower plasma β-carotene levels are linked to an AD diagnosis [78].

The polyphenol benzopyrene compounds known as **coumarins** have anti-inflammatory and anti-cancer properties [83]. They work by boosting signaling

through the antioxidant response element and Nrf2 pathways [84]. The Nrf2/ARE pathway protects the cell by reducing OS which leads to apoptosis. Daphentin, a type of coumarin, is capable of preventing cytochrome c leakage in mitochondria, and loss of membrane potential as well as t-BHP-initiated NLRP3 inflammatory pathways [83]. Coumarins inhibit acetylcholinesterase (AChE) and lead to the reduction in Aβ deposition and β-secretase inhibition [85, 86].

Flavonoids can be found in a variety of fruits, vegetables, wine, tea, cereals, and other plant-based beverages and foods, such as chocolate. They can promote neurogenesis, activate neural regeneration, enhance current neuronal function, and prevent malfunctioning of neurons. They can encourage the removal of Aβ-peptides and prevent tau from being phosphorylated by the mTOR/autophagy signaling. Flavonoids can also be promising symptomatic anti-medicines for AD because of their ability to inhibit cholinesterase [87].

The turmeric, derived from *Curcuma longa*, contains **curcumin**, which has been shown to have anti-amyloid effects in AD. Curcumin can diffuse the BBB and binds to Aβ due to its lipophilic nature. Its neuroprotective efficacy against Aβ toxicity was demonstrated by its ability to inhibit Aβ fibril formation from Aβ monomer, suppress Aβ aggregation, and dismantle the fibril form of Aβ (Fig. 8.4). Additionally, it disaggregated Aβ deposits, inhibited the formation of new Aβ deposits, and decreased the size of the residual Aβ aggregations [88, 89]. It has been shown to suppress β-secretase and AChE activity as well as Aβ aggregation and Aβ-induced

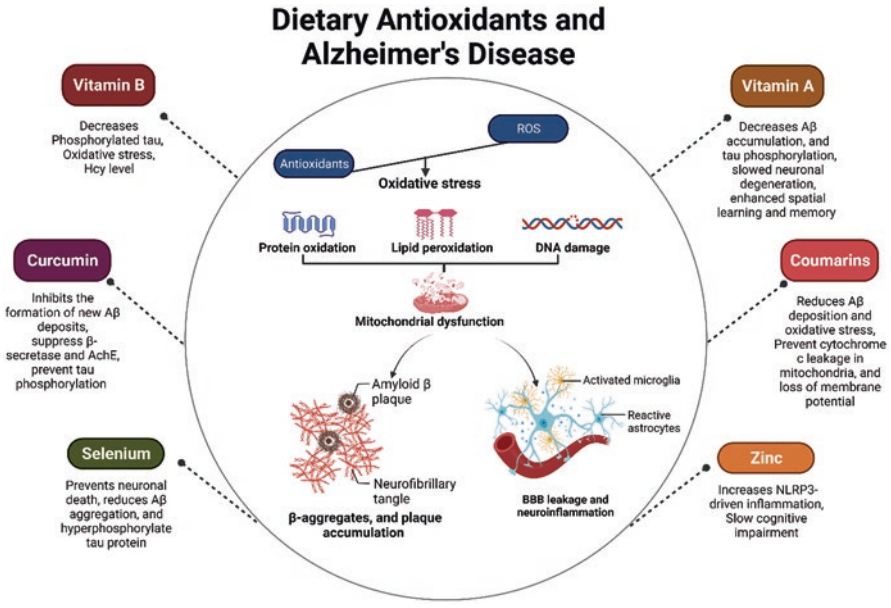

Fig. 8.4 Role of dietary antioxidants in Alzheimer's disease. (*Aβ:* Amyloid β; *AchE:* Acetylcholine esterase; H_2O_2: Hydrogen peroxide; *NLRP-3:* NLR family pyrin domain containing 3; *BBB:* Blood brain barrier; *DNA:* Deoxyribonucleic acid; *ROS:* Reactive oxygen species)

inflammation. Oral administration of curcumin reduces behavioral impairment in animal models of AD and prevents Aβ deposition, Aβ oligomerization, and tau phosphorylation [90].

8.4.2.5 Zinc

Zinc plays multiple roles in AD as both the enzymatic breakdown of the Aβ peptide and the non-amyloidogenic processing of the APP. Zinc binds to Aβ, encouraging its aggregation into neurotoxic species, and zinc homeostasis disruption in the brain causes deficiencies in synaptic function and memory. Consequently, zinc dyshomeostasis may be crucial in the development of AD, and zinc chelation is a potential treatment strategy [91, 92]. Its deficiency exacerbated cognitive impairment in an animal model of AD via increasing NLRP3-driven inflammation [93].

8.4.2.6 Selenium

Selenium (Se) is a biological trace element significant for the functioning of the brain. Consolidated evidence from meta-analyses shows that selenium status is much lower in AD brains than in controls [94]. Se's biological actions are mostly carried out by selenoproteins, which are essential for preserving healthy brain function. Selenoproteins particularly those linked with brain function have a role in the development of AD. The impact of the ER (endoplasmic reticulum)-resident protein SELENOK on Ca^{2+} equilibrium, the receptor-associated synaptic activities, and the role of GPX4 in ferroptosis are explored as putative roles of these selenoproteins in AD [95]. It prevents neuronal death, reduces amyloid β aggregation, and hyperphosphorylate tau protein in the fight against AD [96, 97].

8.5 Antioxidants and Epilepsy

Epilepsy is a chronic, dynamic neurological condition that causes continuing brain damage. The development of epilepsy is influenced by an oxidative injury that leads to neuronal death [98, 99]. Glutamate excitotoxicity, OS, and mitochondrial dysfunction are all contributing factors to epilepsy [100, 101]. Patients with epilepsy suffer from chronic neurological conditions such as spontaneous recurrent seizures and deficits in learning and memory [102, 103]. Epileptogenesis is a collection of events that transforms a normal brain into one that experiences recurrent seizure activity. Neurodegeneration, damage to the BBB, and dysfunction of the glutamatergic system, which is caused by neuroinflammation, are important variables that contribute to epileptogenesis. Hypoxia and OS are also thought to involve in the epigenetic alteration of DNA. In addition, hypoxia can cause the complement system and cytokines to activate, both of which support neuroinflammation. In a

feedback loop, the neuroinflammation in turn triggers the cytokine and complements system production. The convergence of all these mechanisms causes epilepsy to develop [104].

8.5.1 Endogenous Antioxidants

8.5.1.1 Alpha Lipoic Acid

It is an endogenous thiol that occurs naturally in mammalian tissues and functions as a cofactor for α-ketodehydrogenase complexes [105]. ALA can produce endogenous antioxidants such as vitamins C and E and GSH in the body. It prevents DNA damage brought on by peroxynitrite and the production of hydroxyl radicals [106]. After pilocarpine-induced convulsions, antioxidant therapy dramatically decreased nitrite content and lipid peroxidation as well as elevated catalase and SOD activity in the hippocampus of rats [107]. Administration of ALA considerably reduces the frequency of spontaneous seizures [102].

8.5.1.2 Melatonin

One of the most enigmatic compounds made by the human body is melatonin, an indoleamine derivative of serotonin produced in the pineal gland, a region of the epithalamus. By increasing GABA-ergic neurotransmission and decreasing glutamatergic neurotransmission, melatonin also regulates the electrical activity of neurons. Melatonin may reduce seizures in people, and it works best for treating juvenile intractable epilepsy. Additionally, melatonin reduces electron leakage from mitochondria, reducing the production of free radicals. All of these procedures lessen DNA damage, lipid peroxidation, and protein peroxidation [108]. Melatonin and its analogs, which bind to melatonin receptors, are used to control seizures [100]. It lessens the activation of certain proteins in the hippocampal region, including the transient receptor potential (TRP), and glutamate receptors, and regulates excessive OS products, as well as mitochondrial and Ca^{2+} dysregulations in epilepsy [109].

8.5.1.3 Coenzyme Q10

CoQ10 pretreatment reduces spontaneous recurring seizures and prevents hippocampus neuronal death and abnormal mossy fiber sprouting (MFS) by reducing the burden of OS [110]. In epilepsy mouse models, CoQ10 is used as an adjuvant for Anti-epileptic drugs (AEDs) therapy, suggesting that it may lessen seizure severity

and guard against seizure-induced oxidative damage that contributes to the cognitive impairment linked to long-term use of AEDs [111]. In rats experiencing pilocarpine-induced status epilepticus, CoQ10 supplementation reduced RNA oxidation, seizure onset, and neuronal death [112].

8.5.2 Dietary Antioxidants

8.5.2.1 Vitamin E

Vitamin E increases catalase activity in mouse epilepsy models using pilocarpine. A drop in the level of vitamin E has been seen in the cerebral cortex after pilocarpine-induced seizures. Vitamin E and glutathione treatment can decrease neuronal mortality and lipid peroxidation in kindling rat models of epilepsy [71, 113].

8.5.2.2 Vitamin C

Vitamin C can cross the BBB with ease and lessens hippocampal damage during seizures. It strengthens cell membranes and reduces lipid peroxidation and inhibits seizure activity that can lower mortality, depending on the type of seizure [71, 114]. It increases the hippocampal SOD and catalase activities, lengthens the time between the onset of the first seizure, suppresses behavioral seizure episodes, and reduces brain damage [115]. Vitamin E and C supplementation causes a considerable decrease in serum MAD levels and an increase in serum total antioxidant status (TAS), which was accompanied by a reduction in seizure frequency of more than 70% [116].

8.5.2.3 Flavonoids

Flavonoids are present in vegetables, fruits, nuts, and beverages made from plants, traditional eastern remedies, and herbal nutritional supplements. In epilepsy, flavonoids may provide neuroprotection [117]. The flavonoids eugenol, naringin, silibinin, naringenin, hesperetin, and morin have been found to lessen the symptoms of epilepsy. These effects appeared to be occurring via two main mechanisms:

1. The amelioration of hippocampal structural modifications, including through dentate gyrus (DG), granule cell dispersion (GCD), and
2. The inhibition of pro-inflammatory cytokine expression [118].

Naringenin, one of the most prevalent flavanones found in citrus fruits, is found to inhibit OS biomarkers in a rodent model of epilepsy by activating numerous

signaling pathways [119, 120]. Naringenin therapy can minimize the intensity of seizures, decrease lipid peroxidation and ROS production, and restore antioxidant enzymes in the hippocampus of epileptic mice [121].

Polyphenol **resveratrol** lowers ROS production by stifling mitochondrial complex II activity and cytochrome c leakage. It indirectly inhibits OS, apoptosis, and inflammation by activating sirtuin 1, a class III histone deacetylase. It causes inhibition of neurodegeneration, mossy fiber sprouting, astro- and microgliosis, and spontaneous recurrent seizures [112]. By opening voltage-gated sodium channels and activating calcium-activated potassium channels, resveratrol can reduce the activity of cortical neurons and a reduction in the rate at which neurons fire an action potential [122].

Curcumin can lessen seizures, reduce several markers of OS, and stop hippocampus neuronal loss and MFS [123]. It lessens the severity of spontaneous recurring seizures and acts as an inhibitor of NFκB and a strong inducer of the HO-1 protein. These two elements are crucial in the body's OS and inflammation. Through its capacity to reduce the production of several inflammatory indicators, including COX-2, lipoxygenase, and inducible nitric oxide synthase (NOS), curcumin can help treat epilepsy [124]. It also inhibits the expression of α-synuclein and the Wnt/β-catenin, apoptosis, and autophagy pathways in brain regions [125] [126]. Combined usage of curcumin and carbamazepine demonstrates that the powerful antioxidant curcumin can be utilized as an adjuvant in antiepileptic medication [127].

8.6 Antioxidants and Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is first reported by Joffrey and Jean-Martin Charcot. Upper motor neurons (UMN) of the motor cortex, as well as lower motor neurons (LMN) of the spinal cord and brainstem, are selectively lost in ALS [128, 129]. Patients with ALS experience respiratory failure, dysphagia, and muscle atrophy [130–132]. Increased OS is linked to the etiology of ALS, and neuroinflammation is brought on at the pathogenic level by the activation of astrocytes, microglia, and peripheral immune cells [133].

8.6.1 Endogenous Antioxidants

8.6.1.1 Coenzyme Q10

It is known to prevent OS by scavenging free radicals in ALS. When given 50 days after birth, CoQ10 (200 mg/kg daily) dramatically enhanced the cerebral cortex's mitochondrial CoQ10 contents and lengthened the longevity of SOD1G93A

transgenic mice [134]. It also boosts brain mitochondrial concentration and prolonged longevity in the SOD1 transgenic mice [135].

8.6.1.2 Melatonin

Melatonin lowers OS and inhibits apoptotic pathways in ALS [136]. High dosages of melatonin slowed the course of the disease and improved survival rates in ALS [137, 138]. Melatonin (30 mg/kg) is found to delay the onset of disease, neurological degeneration, and death rate [139]. However, melatonin-treated mice displayed increased motor neuron loss, 4-HNE (levels of the lipid peroxidation marker), and upregulation of SOD1 level, indicating that melatonin worsens the disease phenotype in the SOD1G93A model by enhancing toxic SOD1 [140].

8.6.1.3 Glutathione

The redox imbalance of GSH is linked as a significant modulator of enhanced ROS production and death in motor neurons and astrocytes. Its depletion and neuronal toxicity have been linked to mutations in the ALS-causing genes [141]. The GSH reduction in motor neuron cells and the spinal cord is associated with caspase 3 activation, apoptosis-inducing factor (AIF) translocation, and motor neuron deterioration during the progression of ALS-like disease [142]. The activation of ALS-causing genes triggers numerous pathways and regulators that result in a GSH redox imbalance [143]. In SOD1G93A transgenic mice, Nrf2 overexpression in astrocytes improved survival and postponed neuromuscular denervation [141, 144, 145].

8.6.1.4 Superoxide Dismutase

More than 180 mutations in the SOD1 gene's coding area and several others in its non-coding regions have been found in ALS patients [146]. These mutations cause a decrease, maintenance, or increase in dismutase activity when compared to SOD1 in its wild-type state [140]. Motor neurons that express mutant SOD1 are vulnerable to OS-induced cell death [147, 148]. The calcium-binding ER chaperone calreticulin is present at reduced levels in motor neurons. The activation of the Fas/NO pathways in motor neurons requires a reduction in the expression of this protein, which is both required and sufficient [149].

8.6.1.5 Catalase

In transgenic fALS mice, catalase was modified with putrescine to help it better traverse the BBB, delaying the development of disease signs [150]. This antioxidant did not delay the onset of the disease in SOD1G93A animals, but it does show that avoiding peroxide-mediated mitochondrial damage stops the disease [151].

8.6.2 Dietary Antioxidants

8.6.2.1 Vitamin E

Long-term vitamin E supplementation has been linked to lower ALS rates, and a study found a non-significant reduction in ALS risk in men who received α-tocopherol supplementation (50 mg/day) [132]. Vitamin E is mostly obtained from legumes, and regular use of this vitamin is linked to a lower risk of death in ALS patients [152, 153]. Preclinical research with SOD1G93A transgenic mice revealed that vitamin E supplementation (200 UI/kg) reduced the beginning of the disease and delayed its progression, but had no effect on survival time [154]. Patients taking α-tocopherol and riluzole for 3 months showed a decline in plasma TARS and an elevation in GSH levels [130].

8.6.2.2 Carotenes

Carotenes are natural pigments that give fruits and vegetables their orange, red, yellow, or green color. They also have antioxidant and ROS-neutralizing capabilities [155, 156]. Carotenoid intake delays the onset of ALS; nevertheless, case-control research involving 77 Koreans who had been diagnosed with the disease found a negative correlation between ALS and dietary intake of carotenes [132]. β-carotene can be used to treat apoptosis and neuroinflammation in ALS patients [157]. Patients with ALS who regularly take carotenoid supplements have higher survival times [153].

8.6.2.3 Phenols

A strawberry extract rich in anthocyanins, with the main ingredient being callistephin, delayed the onset of ALS, preserved grip strength, and extended longevity in SOD1G93A mice [158, 159]. **Fisetin** (9 mg/kg) improves motor capabilities, delayed the start of the disease, and increased longevity in SOD1G85R *Drosophila melanogaster*, and SOD1G93A mice. The ERK pathway is stimulated to control cell survival and appears to be the main signaling pathway behind the activity of fisetin [160]. **Quercetin** is found to lessen mitochondrial damage and reduces

neuronal death and inhibit the assemblage and misfolding of SOD1 linked to ALS [161].

Resveratrol exhibits beneficial effects through increasing sirtuin 1 (SIRT1) expression in ALS [162]. It maintains lower and upper motor neuron function and enhances the mitochondrial activity of muscle fibers. It restores the down-regulated AMPK/SIRT1 signaling that was present in the bone marrow mesenchymal stem cells (BMSCs) of ALS patients [132]. It increases survival and postpones the start of ALS [160, 163].

Fruits, coffee, tea, and grains contain phenolic acids. They make intriguing possibilities for improved ALS therapy because of their variety of neuroprotective properties. **Protocatechuic acid** (100 mg/kg) increases survival, enhances motor function, and lowers gliosis in SOD1G93A mice [164]. **Gallic acid** and **wedelolactone** can enhance motor learning capacities and locomotor function in ALS. Both work by decreasing inflammatory cytokines, causing normalization of L-glutamate levels, and reducing caspase-3 activation [165]. **Rosmarinic acid**, the primary component of rosemary extract, improved motor function, prolonged longevity of SOD1G93A mice, and decreased weight loss [166]. **Caffeine acid phenethyl ester** (CAPE) stimulated the antioxidant response element while deactivating the OS-associated NFκB release and delayed the course of symptoms and lengthened survival which leads to a decrease in phospho-p38 levels and glial activation [167].

8.6.2.4 N-Acetyl-L-Cysteine

N-acetyl-L-cysteine (NAC) restores depleted GSH pools, and plasma levels of cysteine, and reduces the effects of free radical damage. It also reduces mitochondrial ROS production, restores the MTT level, and also boosts ATP levels in SH-SY5Y cell lines with the G93A SOD1 mutation. Furthermore, NAC (2 mg/Kg/day) treatment dramatically increased motor function and prolonged survival in SOD1G93A transgenic mice [140].

8.7 Antioxidants and Multiple Sclerosis

The CNS is affected by the chronic inflammatory autoimmune illness known as multiple sclerosis (MS). ROS are crucial in several processes that underlie the pathophysiology of MS. The CNS is equipped with a defense mechanism that includes enzymatic and non-enzymatic antioxidants to counteract the harmful effects of ROS. Antioxidants are used in MS and other autoimmune and inflammatory illnesses because OS is one of the most significant elements of the inflammatory process, which causes myelin breakdown and axonal damage [168, 169].

Clinically, inflammatory and OS mediators, including cytokines like IL-6, IL-1β, IL-17, INF-γ, and TNF-α have been linked to the progression of MS. Dietary antioxidants are found to control immune-inflammatory cell activation, which would

reduce inflammation. They can also reduce OS, which would stop persistent demyelination and axonal damage [168, 170].

8.7.1 Endogenous Antioxidants

8.7.1.1 Glutathione

Active demyelinating MS lesions have considerably higher GPx gene expression. Elevated ROS is linked to the concentration of oxidized glutathione (GSSG) and the concurrent decline in α-tocopherol levels in the blood. The blood of MS patients with the progressive form had significantly higher levels of GSH in addition to GSSG as a compensatory mechanism that protects cells from further oxidative damage. During MS exacerbations, GSH oxidation is also enhanced in patients' cerebrospinal fluid (CSF). Oligodendrocytes are more susceptible to oxidative injury due to their inherently low GSH levels.

The loss of GSH, iron accumulation, mitochondrial dysfunction, and increased ROS production lead to elevated levels of protein carbonylation in MS. The substantial carbonylation of brain proteins can be produced by rapid GSH depletion. This effect is caused by the iron-catalyzed production of hydroxyl radicals from H_2O_2. As a result, the absence of GSH alone results in OS that is sufficient to generate protein carbonyls in addition to lipid peroxides. The findings imply that glutathione therapy is an effective treatment for neuroinflammatory illnesses like MS.

8.7.1.2 Superoxide Dismutase

Inflammatory circumstances that result in excessive TNF-α production are linked to the increased OS and antioxidant enzyme inhibition, most notably reduced SOD1 expression. SOD1 gene expression has been noticeably increased in actively demyelinating lesions in MS. The SOD1 activity in the erythrocytes of MS patients was also significantly reduced, which points to weaker enzymatic defense mechanisms against OS. In guinea pigs with Experimental autoimmune encephalomyelitis (EAE), SOD2 was found to have increased expression, but not SOD1.

8.7.1.3 Catalase

H_2O_2 affects oligodendroglia and can travel in the perivascular space and cause myelin and lipid peroxidation at distant locations in the interstitial optic nerve. Catalase in the CNS prevents the buildup of H_2O_2 and demyelination. Catalase treatment markedly decreased demyelination of the optic nerves and reduced neurological EAE symptoms. It has recently been revealed that combining the removal of

superoxide by extracellular SOD (EC-SOD) and H_2O_2 significantly reduced experimental ocular neuritis in EAE [169].

8.7.1.4 Melatonin

Melatonin, which the pineal gland normally produces at night, is created outside the body from tryptophan. Meat, salmon, milk, eggs, nuts, seeds, soy products, and almonds are the main sources of melatonin. It promotes the production of SOD and glutathione peroxidase (GPx), particularly in SPMS (secondary progressive MS) patients [138, 171].

8.7.2 Dietary Antioxidants

8.7.2.1 Phenols

Curcumin can suppress proinflammatory cytokines and the infiltration of inflammatory cells into the CNS [172, 173] Additionally, macrophages and monocytes contribute to the production of COX-2, iNOS, macrophage inflammatory protein (MIP-1α), monocyte chemoattractant protein 1 (MCP-1) in the presence of curcumin while IL-12, IL-8, IL-6, IL-2, and IL-1 are inhibited by curcumin supplementation. It prevents the cytokines from mediating NF-κB pathway activation by inhibiting Akt (protein kinase B) and IκB (inhibitor of kappa B) through a variety of inflammatory stimuli. It also reduces the expression of NF-κB regulated gene products, such as IL-17, IL-1β, prostaglandin E2, MIP-1α, and TNF-α. It reduces the BBB disruption brought on by Th17 cells due to its role as an NFκB pathway inhibitor [170].

Resveratrol prevents neutrophils from producing the pro-inflammatory metabolites 5-LO and 15-LO, which are part of the arachidonic pathway. In EAE-induced mice, resveratrol was found to significantly reduce the levels of several cytokines and chemokines, including IFN-γ, TNF-α, IL-17, IL-12, IL-9, IL-2, as well as MCP-1, MIP-1α, and chemokine (C-C motif) ligand 5 (CCL5). It alters the synthesis of eicosanoids or blocks the COX-2 and iNOS pathways by inhibiting AP-1 or NF-κB. It was shown that in an EAE animal model, resveratrol decreased the inflammatory responses and clinical symptoms, which was mainly due to the reduction of pro-inflammatory mediators and triggering the apoptosis in activated T cells in the spinal cord [170].

Of the biologically active catechins found in green tea, **EGCG** is the most prevalent. Purified EGCG (95 percent) lessens the severity of EAE by lowering the severity scores, which were linked to lowered immune cell infiltrates, decreased demyelination in the spinal cord, and lowered levels of inflammatory cytokines that support Th1 and Th17 differentiation. Additionally, it improves hippocampus cell survival and development [174].

8.7.2.2 Vitamin D

In addition to supporting calcium homeostasis and bone health, vitamin D is important for immune regulation and the reduction of OS. A low measure of vitamin D leads to an increased possibility of MS development and relapse. Vitamin D possesses immunomodulatory and anti-inflammatory effects on the pathogenetic pathways of MS by preventing the development of CD4+ T cells, hence reducing the likelihood of developing MS and slowing the course of the illness.

8.7.2.3 Vitamin A

It is a fat-soluble substance that plays a number of roles in immunity, skin, and vision. Retinoids and carotenoids, which are components of vitamin A, can be found in milk, liver, cheese, green leaves, oil, fruits, and vegetables. A low quantity of vitamin A in plasma is associated with an increased probability of MS development. Patients with MS who are supplemented with high dosages of vitamin A (400 IU/day), show improvements in their fatigue, depression, and cognitive state [175].

8.7.2.4 Vitamin E

Vitamin E is found to have immunomodulatory effects on several immune cells. By lowering macrophages' production of the T cell inhibitory prostaglandin E2, it improves naive T cell activity. It is necessary for the proper operation and communication between T regulatory cells, dendritic cells, and CD8+T cells. It also appears to downregulate certain adhesion molecules (molecules that allow lymphocytes to travel past the BBB) and lowers the chance of getting MS [1].

8.7.2.5 Alpha Lipoic Acid

It scavenges ROS, chelating copper and iron, raising vitamin C and GSH levels, and healing OS damage. It has immunomodulatory properties as well. It increases the cAMP synthesis and decreases IFN-γ generation. It can also prevent the migration of macrophages, inflammatory T cells, and monocytes into the spinal cord and brain, possibly by lowering the expression of ICAM-1 and VICAM-1 by CNS endothelial cells, inhibiting the enzymes known as matrix metalloproteinases (MMPs), and lowering BBB permeability, thus can be used as a therapeutic strategy in several disorders, especially MS, AD, and diabetic neuropathy [1]. It inhibits monocyte infiltration into the CNS by lowering monocyte migratory potential and enhancing BBB integrity against OS attacks. A recent clinical trial that was double-blind, randomized, and controlled showed an improved TAC level after the daily intake of ALA (1200 mg/day) for 12 weeks in a group of MS patients [176].

8.7.2.6 Fatty Acids

One study found that MS incidence was low in those who consumed diets high in PUFAs. According to the findings of meta-analyses, PUFAs are ineffective at stopping the progression of the disease but may lessen the number of relapses. In human research, PUFAs are linked to a better quality of life, a minor improvement in relapse rat health, and a lower quantity of disability as measured by the Expanded Disability Status Scale (EDSS) [175, 177]. In contrast to the quality of life, EDSS score, or fatigue, a different study showed that PUFAs improved certain markers associated with inflammation and/or neurodegeneration in MS patients [178].

One PUFA with a low incidence of MS is α-linolenic acid. It can support the immune system by lowering inflammation-related indicators. MMP-9 levels in MS patients can also be reduced by eicosapentaenoic and docosahexaenoic acids (EPAs and DHAs). Fish oil supplements that are high in omega-3 fatty acids help MS patients by reducing their levels of MMP-9 and inhibiting its expression and also reducing inflammation and OS. By reducing proinflammatory cytokines and free radicals, omega-3 fatty acid supplementation enhances the quality of life of MS patients by lowering relapse rates [179, 180].

8.8 Antioxidants and Schizophrenia

Schizophrenia is a severe and crippling mental illness with an estimated 0.75 percent lifetime prevalence worldwide. The long-term effects of this condition are frequently negative, and even receiving treatment, people with schizophrenia have a three times higher risk of dying young than the general population. Positivity, negativity, and disorganization are signs of schizophrenia. Hallucinations and delusions are examples of positive symptoms and motivational decline, apathy, and social retrieval are negative signs. Numerous cellular structures have been observed to suffer oxidative damage as a result of elevated ROS levels and depleted antioxidant defenses. It has been demonstrated that patients with non-medicated, medicated, first-episode and chronic schizophrenia have reduced levels of TAC and glutathione in their plasma. Additionally, schizophrenia patients' peripheral tissues have been discovered to have higher quantities of ROS in addition to lower levels of SOD and GPx [181].

A higher quantity of 8-hydroxydeoxyguanosine, a marker of DNA damage and cell death, as well as protein carbonylation, have all been seen in schizophrenic patients. Increased OS can result in from impairments in catalase, SOD, glutathione, and GPx, as well as thiobarbituric acid reactive substances (TARS) and MDA, and decreased antioxidant levels in the red blood cells (RBC), cerebrospinal fluid, plasma, and serum. Additionally, ROS production can also rise due to mitochondrial dysfunction, dopamine auto-oxidation, and the pro-oxidant properties of several antipsychotic drugs [182].

8.8.1 Endogenous Antioxidants

8.8.1.1 Superoxide Dismutase

Schizophrenic patients have faced both enhanced and decreased SOD activity. It's likely that when the condition worsens, SOD levels increase as a protective measure against OS. Its activity is considerably reduced in RBC specimens from schizophrenia patients. An altered antioxidant defense system in addition to abnormalities in the peripheral activity of SOD has been shown in schizophrenic patients. The frontal and temporal cortex has been found to have an elevated level of Mn-SOD with no change in Zn or Cu-SOD. An increase in Cu, Zn, and Mn-SOD was seen in the substantia innominata regions and frontal brains of schizophrenia patients.

8.8.1.2 Glutathione Peroxidase

It is associated with the elimination of H_2O_2 and other peroxides using GSH. When compared to control subjects, first-episode schizophrenia patients with drug naiveness had significantly higher plasma GPx activity. Additionally, GPx activity was shown to be lower in RBC samples from schizophrenic patients but plasma samples from both neuroleptic-naive and long-term neuroleptic-free showed higher GPx activity.

8.8.1.3 Catalase

Catalase activity did not change in leukocytes, it was shown to be much higher in the erythrocytes of schizophrenia patients. Additionally, compared to control participants, drug-naive first-episode schizophrenia patients had significantly lower plasma CAT activity [183, 184].

8.8.2 Dietary Antioxidants

8.8.2.1 Vitamin E and Vitamin C

Vitamin E and C are seen to avoid oxidative damage and the aggravation of symptoms in schizophrenia. The majority of ROS are produced in the nucleus, mitochondria, cytosolic proteins, and nucleus, where vitamin E has a limited ability to counteract oxidative damage. Vitamin C protects neurons from OS, ensures normal neurotransmission control, reduces inflation, and modifies neuronal development and epigenetic function. Vitamin C can not only reduce membrane phospholipid peroxidation but also improve vitamin E regeneration. It's interesting to note that vitamin C levels in the brain are 10 times greater than in serum, and it can pass past

the BBB and remain there by way of the glucose transmitter GLUT1. SOD and vitamin C measures are considerably lower in schizophrenia patients than in healthy controls.

Schizophrenia patients show higher serum MDA levels and lower plasma ascorbic acid levels. Vitamin C supplementation combined with atypical antipsychotics can reduce OS, and raise ascorbic acid levels. Vitamin C treatment alone or in conjunction with vitamin E significantly lowers total dyskinetic movement scores and improves Brief Psychiatric Rating Scale (BPRS).

8.8.2.2 Vitamin D

Vitamin D is frequently inadequate in schizophrenia patients. Vitamin D modulates neurotrophin synthesis, calcium homeostasis, neuro mediators synthesis, and reduces oxidative damage. It is seen that lower levels of vitamin D lead to cognitive dysfunction and more severe symptoms in schizophrenia [184].

8.9 Antioxidants and Stroke

A stroke is a neurological deficit caused by an acute, focused injury to the CNS caused by intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and cerebral infarction. It is a leading cause of disability and death worldwide [185]. An important mechanism of cell damage during cerebral ischemia is OS, which is caused by excessive formation of ROS or defective metabolism [186]. According to research and clinical investigations, OS is a major factor in brain damage that occurs after a stroke [187]. Overproduction of ROS occurs in OS and causes damage to neurons and kills cells [188, 189].

8.9.1 Endogenous Antioxidants

8.9.1.1 Bilirubin

It is the most powerful endogenous antioxidant and increases in various OS conditions, including stroke. It is a byproduct of heme metabolism and can affect the occurrence and prognosis of ischemic stroke [190]. Although all bilirubins have some antioxidant qualities, only unbound, bioactive bilirubin can pass the BBB and be used to treat ischemic strokes [191]. Using tertiles of bilirubin, this study included 13,214 patients and evaluated the risk of stroke linked with an increase in total bilirubin level of 1.71 mol/L [192]. This study found that total bilirubin levels were positively correlated with stroke outcomes in participants with a history of stroke and negatively correlated with stroke prevalence [193].

8.9.1.2 Uric Acid

It scavenges hydroxyl radicals, superoxide anion, hydrogen peroxide, and peroxynitrite and acts as a powerful antioxidant in human plasma. Preclinical investigations in hyperglycemic mice showed improved stroke outcomes after UA therapy. In healthy volunteers, IV injection of UA enhanced serum free-radical scavenging ability both at rest and during intense physical activity and eliminated lipid peroxidation [194, 195].

8.9.2 Dietary Antioxidants

8.9.2.1 Vitamin E

People with high dietary vitamin E consumption have a 17 percent lower risk of stroke compared to those with low dietary vitamin E intake. Vitamin E exhibits its capacity to protect cell membranes by scavenging ROS and inhibiting lipid peroxidation [196, 197].

8.9.2.2 Vitamin D

Individuals who obtained vitamin D experienced a notable improvement in their stroke prognosis after three months [198]. Vitamin D insufficiency is linked to an increased risk of ischemic stroke, with hypertension, diabetes mellitus, hyperlipidemia, and ischemic heart disease as contributing factors [199]. Vitamin D insufficiency was independently linked to ischemic stroke in both major artery atherosclerosis and cardiac embolic stroke [200].

8.9.2.3 Vitamin C

In view of the randomized controlled trials findings that vitamin C had no adverse impact on preventing stroke [201]. Plasma vitamin C levels are inversely correlated with the incidence of stroke and can be used as a preventive component [202].

8.9.2.4 Omega-3 Fatty Acids

Since mammals cannot produce omega-3 fatty acids, they must obtain them from their diet. Three different kinds of omega-3 PUFAs are present: α-linolenic acid, DHA, and EPA. In both adult and newborn animal models, all fatty acids exhibit a

neuroprotective effect against brain damage brought on by experimental stroke [203]. They are particularly crucial for the human brain, and a lack of them increases the chance of developing several illnesses [204]. The severe deficiency of omega-3 fatty acids in the diet can enhance the probability of stroke [205].

8.9.2.5 Phenol

They work by blocking xanthine oxidase, reducing the production of hypoxanthine, xanthine, oxygen radicals, raising the levels of MDA, reducing glutathione, and leading to cause a reduction in OS in stroke patients [206]. They prevent stroke by protecting the integrity of the endothelium and counteracting the harmful consequences brought on by ionic imbalance, excitotoxicity, and the production of ROS [207]. The risk of ischemic stroke is inversely correlated with flavanone intake [208]. Specific flavonoids and their physiologically active metabolites have positive effects on platelet function, inflammation, thrombosis, and protection against ischemia-reperfusion injury and arrhythmia [209].

8.10 Antioxidants and Brain Cancer

The growth and survival of primary CNS cancers such as medulloblastoma, glioblastoma multiforme, and ependymoma depend on the presence of cancer propagating cells (CPCs). These cells also referred to as BCPCs (brain cancer propagating cells), can regenerate and multiply. The evidence is mounting that neural stem cells (NSCs) and their progenitors may undergo metamorphosis to become BCPCs. [210] An intracranial neoplasm known as a brain tumor can develop in either the brain or the central spinal canal. Most adult brain tumors are secondary or metastatic tumors, meaning that they can develop from cancers that are primarily found in other organs but have moved to the brain [211, 212].

The development of brain tumors has been linked to OS, which is expressed by an imbalance between the generation of free radicals and antioxidant defenses [213]. In these circumstances, both endogenous sources (peroxisomes and mitochondria, but also neurotransmitter oxidation or inflammatory cell activation) and exogenous sources (environmental factors, medications, irradiation, and chemicals) may produce excessive amounts of free radicals [214]. ROS may play a role in a variety of stages of carcinogenesis, including initiation, progression, angiogenesis, and metastasis [215]. The increasing quantity of ROS that results in tumor formation involves not only oxidative aggression but also a diminished response to antioxidant defenses. Both endogenous enzyme and non-enzymatic antioxidant systems work to avoid or lessen the harm done by too many free radicals [213].

8.10.1 Endogenous Antioxidants

8.10.1.1 Superoxide Dismutase

The majority of brain tumor types have elevated Mn-SOD expression, which is associated with a bad prognosis. In the proliferative stage, it appears to be a tumor suppressor. It is increased when a tumor develops more quickly [216] [217]. ROS levels are necessary for tumorigenesis and metastasis. Low Mn-SOD levels make cells more susceptible to OS, which can cause them to develop into tumor cells [218].

8.10.1.2 Glutathione

The main endogenous neuroprotectant for the brain is GSH. GSH shields brain cells from oxidative damage caused by peroxynitrite and lipid peroxidation in neuron cells [217]. Some brain tumors respond more favorably to certain chemotherapeutic agents than others, and this sensitivity is influenced by GSH and the GSH enzyme-linked system. The GST-p isoform, GSH metabolic pathway enzyme, has received the most attention as a crucial indicator of the effectiveness of chemotherapy in treating brain tumors. Drug resistance in primary brain tumors is significantly influenced by the interaction between Mrp-facilitated efflux of the GSH-drug conjugate and GSH/GST-mediated drug detoxification. This interaction provides a promising target for therapeutic approaches aimed at selectively modulating drug sensitivity [219].

8.10.1.3 Catalase

Catalase has a protective and anti-apoptotic effect in cells by removing ROS [220]. Brain tissue from rats with N-Ethyl-N-nitrosourea-induced gliomas had decreased levels of CAT activity. On the other hand, many brain cancers have shown much-increased catalase activity [221].

8.10.1.4 Glutamate

Numerous neurological diseases have been linked to glial Glutamate transport deficiency. Its uptake into astrocytes was compared to that of their cancerous counterparts, it was shown that Glutamate uptake into gliomas was virtually absent [222]. It activates metabotropic glutamate (mGlu) receptors that control the proliferation of BSPCs (brain stem-progenitor cells). Specific mGlu receptor subtypes are fresh prospective targets for the therapy of several malignant cancers, such as brain tumors [223, 224].

8.10.2 Dietary Antioxidants

8.10.2.1 Vitamin-E

All individuals with Grade III malignant gliomas have higher survival rates when they consume more vitamin E. Antioxidants, such as vitamins C and E, have been proven to lower the risk of brain cancers in children whose mothers took these nutrients throughout pregnancy [225]. Except for individuals with acoustic neurinoma, most patients with brain tumors tended their plasma levels of vitamins A and E to decline.

8.10.2.2 Retinoid

Retinol's ability to scavenge free radicals has long been recognized as making it an excellent antioxidant. Low amounts of retinol and β-carotene were seen in cancer patients. Initially, the theory that certain malignancies were related to an underlying vitamin A shortage led to the use of retinoids as a treatment for those illnesses [226]. In gliomas, retinoid receptor expression may become imbalanced as a result of environmental stimuli that boost glial cells' endogenous production of retinoic acid (RA). The promising novel therapeutic approach for gliomas is the combination use of RAR-agonist and RAR-antagonist, maybe even at a late stage of the disease. This theory predicts that the RAR-antagonist would prevent RAR-induced gliomas, while the RAR-agonist would slow the growth of tumors and aid in the regeneration of healthy glia [227]. Additionally, fat-soluble vitamins like vitamin A and vitamin D played a part in prevention by controlling cell differentiation and reducing the growth of cancer cells [228, 229].

8.10.2.3 Vitamin C

By removing free radicals and promoting apoptosis, several vitamins with antioxidant qualities, like vitamin C and vitamin E, have been found to slow the growth of tumors [230]. A recent meta-analysis indicates that larger intakes of vitamin C, β-carotene, and folate significantly reduced the risk of developing brain tumors [231]. On the other hand, the rat experiment discovered that rats administered vitamin C had higher levels of indicators linked to the proliferation of brain tumors, such as platelet-derived growth factor receptor (PDGF-R) [232].

8.11 Conclusion

Oxidative stress is a chief player in the pathophysiology of several brain disorders, including AD, HD, PD, ALS, MS, epilepsy, schizophrenia, stroke, and brain cancer. It causes protein, lipid, as well as DNA damage due to the creation of highly reactive chemicals like hydroxyl and peroxynitrite radicals. In the brain, endogenous enzymatic and non-enzymatic antioxidants such as glutathione, glutathione peroxidase, superoxide dismutase, melatonin, uric acid, and bilirubin act as a strong defense system against these processes. In addition to endogenous enzymes, all dietary antioxidants effectively maintain neuronal morphology and cell viability by restoring mitochondrial activity and lowering ROS levels in the brain. Fruits and vegetables including grapes, oranges, cherries, blueberries, lemon, tomatoes, and dairy products such as eggs, milk, fish, meat, and nuts are rich sources of dietary antioxidants. The intake of fruits, vegetables, grains, and nuts in a balanced fashion act as the most efficient strategy for people to boost their antioxidant as well as anti-inflammatory capability, and lower their chance of acquiring brain disorders. Hence, dietary antioxidants appear to be useful component for both therapeutic and preventive approaches to a variety of brain disorders.

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