Antioxidant Nutraceuticals against Neurodegenerative Disease

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This entry discusses on selected nutraceuticals and their plausible antioxidant effects on Alzheimer and Parkinson disease. Nutraceuticals such as resveratrol, curcumin and vitamin E alleviate oxidative stress by scavenging free radicals, metal chelators, and enhance antioxidant enzymes. Additionally they regulate intracellular signaling such as inflammatory, survival and apoptotic pathways.

Keywords: Antioxidant Nutraceuticals against Neurodegenerati ; oxidative stress ; free radical scavenger ; metal chelator ; antioxidant enzymes ; inflammation ; cell survival ; apoptosis

1. Introduction

Neurodegenerative disease is an irreversible condition where the function of neurons declines over time that leads to neuronal death. The incidence rates increase every year, especially in countries with an ageing population. Common neurodegenerative diseases include Alzheimer (AD) and Parkinson (PD) diseases. Worldwide, there are approximately 50 million people living with dementia, with 60–70% diagnosed with AD[1] [1]. In America, 5.8 million individuals over the age of 65 has AD, and this is projected to increase by 6.7% between 2020 and 2025[2] [2]. PD is the second most widespread neurodegenerative disease after AD, and affects movement. The prevalence of PD is approximately 2% of the population older than 65 years old, involving 6.1 million people in 2016 globally[3] [3]. Although AD and PD affect different areas in the brain and display distinctive clinical features, they share a strikingly similar pathophysiology mediated by oxidative stress.

1.1 Alzheimer and Parkinson Disease

AD is a brain disorder characterized by a progressive and irreversible decline in cognitive function attributed to the anomalous accumulation of neurofibrillary tangles and amyloid plaques in the brain[1]. Extracellular senile plaques (SP) and neurofibrillary tangles (NFT) are pathological hallmarks of AD. SP is generated by the fibrils of the beta-amyloid peptide (Aβ) from the proteolysis of amyloid precursor protein (APP), a transmembrane glycoprotein, by the β- and γ-secretase[4][5]. Neurofibrillary tangles (NFT) can be seen in neuron cells, which are composed of paired helical filaments (PHF) that self-aggregate due to hyperphosphorylation of tau proteins [[5][6]. Recent evidence indicate that amyloid depositions occur 15–20 years before the onset of dementia, after which tau pathology develops[7][8][9]. Nevertheless, the molecular mechanism that drives the accumulation of these protein aggregates remains poorly understood, especially in sporadic cases, which hinders us from finding the right therapy for AD. Numerous evidence has shown that there is a substantial elevation of oxidative stress in AD brains, which is believed to be fundamental in the development of the disease[10] [10]. Furthermore, Aβ oligomers, which are the precursor to amyloid fibril, display strong neurotoxicity, and the neurotoxicity is mainly due to oxidative stress induced by toxic conformer of amyloid oligomers in addition to other neurotoxic damage such as neuronal membrane disruption, microglia and astrocyte activation, as well as Ca^{2+} dyshomeostasis[11][12]. Using multiphoton imaging, researchers observed a direct association between free radical production and the existence of amyloid plaques both in AD mouse models and in human AD brain tissues, where fluorogenic free radical indicators was significantly reduced after administration of synthetic antioxidant (287.2 ± 145.6 vs. 163.5 ± 104.3, $p < 0.001$)[13]. Indeed, AD brains display elevated rates of oxidative damage, including protein, deoxyribonucleic acid (DNA), and lipid oxidation, along with the presence of redox-active metals[14].

Parkinson disease (PD), on the other hand, is clinically characterized by four cardinal motor symptoms, including bradykinesia, rigidity, resting tremor, as well as postural and gait difficulty[15]. In PD brains, there is a selective dopaminergic neuronal loss located at the substantia nigra pars compacta, and to a lesser extent in the globus pallidus, putamen, and caudate nucleus. As a result of degenerated neurons in the nigrostriatal pathway, the neurotransmitter dopamine release is reduced[16]. In the neurons of PD, aggregates of abnormal proteins are identified as Lewy bodies. They are parts of the α-Synuclein (α-Syn) protein, which is abundant in the nervous system, but has poorly understood

functions[17]. α-Syn fibrillation forms aggregates that will occupy a large space in the neuron and will eventually cause neuronal death[18]. Similar to AD, oxidative stress plays a central role in the pathophysiological mechanisms underlying PD[19]. The presence of oxidized lipids, proteins, and DNA in substantia nigra of PD patients provide evidence of oxidative stress involvement[20][21]. Furthermore, dopamine metabolism by monoamine oxidase (MAO) produces hydrogen peroxide, while auto-oxidation of dopamine generates superoxide anion and reactive quinones. These reactive molecules exert cytotoxicity not only in dopaminergic neurons, but also other surrounding neurons[22].

The debilitating effects of neurodegenerative disease warrant the search for therapeutic strategies that could delay the disease progression, restore neuronal function, and reduce neuronal death. However, there is still no definitive treatment for neurodegenerative diseases, while the treatment mainly focuses on improving the symptoms. Therefore, the potential benefits of nutraceutical compounds as neuroprotective agents against oxidative stress in neurodegenerative diseases are worth exploring. Nutraceuticals are defined as foods or food-based products containing natural bioactive compounds that promote good health with the ability to prevent and treat a wide variety of diseases and disorders[23]. The naturally occurring antioxidants found in food includes vitamins, alkaloids, and polyphenols (flavonoids, phenolic acid, and stilbenes). Neuroprotection of nutraceuticals is mediated by its antioxidant, anti-inflammatory, calcium antagonist, and anti-amyloidogenic properties. The potential of nutraceutical as neuroprotective agents has gained worldwide interest due to its availability, better tolerance, and fewer side effects. The antioxidative effects of nutraceuticals on neurodegenerative diseases are attributed to its ability to scavenge free radicals, prevent biomolecules (lipid, DNA, and protein) damage, inhibit free radical generating enzymes, activate internal antioxidant enzymes, chelate metal ions, and regulate signaling pathways that are important for cell survival[24].

2. Free Radicals and Oxidative Damage to Biomolecules

2.1. Free Radical Formation

The levels of free radicals or reactive species have been found to increase in age-related neurodegenerative disorders. Under normal conditions, low to moderate concentrations of reactive oxygen species (ROS) act as a defense mechanism in cell injury, innate immune response, regulate oxygen homeostasis, mediators in cell signaling including cell proliferation, differentiation, and apoptosis[25][26][27]. Nonetheless, elevated free radical formation can lead to neuropathophysiological conditions in oxidative stress. Significantly high ROS levels were reported in AD patients as well as in vitro and in vivo Alzheimer's models[28][29][30]. In oxidative stress, there is an imbalance between oxidants and antioxidants in favor of the former that leads to cell damage[31] [31]. The levels of pro-oxidants from the ROS, including superoxide oxygen radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\bullet}$), as well as reactive nitrogen species (RNS), including nitric oxide (NO) and peroxynitrite ($ONOO^-$), are elevated. In contrast, the levels and activities of antioxidants such as glutathione peroxidase (GPX), superoxide dismutase (SOD), glutaredoxins, thioredoxins (TRX), catalase (CAT), vitamin E, and ascorbate are decreased [31,32]. In neurodegenerative diseases, mitochondria respiration is the most significant contributor of ROS[32][33]. To meet the high energy demand in the brain, glucose uptake by neuronal cells will undergo glycolysis, where the end-product pyruvate enters into the mitochondria[34]. Pyruvate is then metabolized through the pyruvate dehydrogenase and tricarboxylic acid (TCA) cycle and subsequently underwent oxidative phosphorylation in the electron transport chain (ETC) to produce ATP in the presence of oxygen. In normal conditions, approximately 0.2–2.0% of the electron leak out mainly from complex I, formed by nicotinamide adenine dinucleotide (NADH) dehydrogenases containing iron-sulfur centers, and complex III, which consist of cytochrome oxidase, which interacts with oxygen to produce $O_2^{\bullet-}$ and H_2O_2[35]. To prevent oxidative stress, intracellular antioxidant defenses play an essential role in maintaining the cell homeostasis by degrading the ROS. Mitochondria have two SOD isozymes, the manganese superoxide dismutase (MnSOD), or SOD2, in the matrix and the copper/zinc superoxide dismutase (Cu/ZnSOD), or SOD1, in the cytoplasm and intermembrane space that catalyze the dismutation of two $O_2^{\bullet-}$ to form H_2O_2[36] . H_2O_2 is then neutralized into water by GPX enzyme that couples the reaction with glutathione oxidation from reduced glutathione (GSH) to oxidized (GSSG) form. GSSG is then reduced back to GSH by the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent glutathione reductase (GR)[37] [37]. The detoxification of H_2O_2 and $O_2^{\bullet-}$ is vital to prevent the formation of highly reactive $OH^{\bullet}$ via the Fenton reaction in the presence of transition metals[38][39].

2.2. Brain Susceptibility to Oxidative Damage

The brain is highly vulnerable to oxidative stress because it uses a large amount of energy to maintain the neuronal synaptic activity, membrane potential and neurotransmitter synthesis, among other functions. Normally, it uses 20% of the total oxygen metabolism for energy production, even though the organ represents only 2% of the total body weight[40]. Furthermore, it is enriched with polyunsaturated fatty acids (PUFAs) that are particularly susceptible to lipid

peroxidation[41][42]. Lipid peroxides (LPO) are highly reactive molecules that include malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), acrolein, isoprostanes (IsoPs), and neuroprostanes (neuroPs), which are capable of disrupting proteins and DNA structures and functions[43][44][45]. Increased MDA, IsoPs, and HNE have been observed in the brain tissues of Tg2576 AD mice model and post-mortem AD brains [46][47]. HNE stimulated neuronal death by modifying the membrane ion transporter and various neuronal enzymes that impaired the neuronal Ca^{2+}, glutamate, and glucose transport [48]. Apart from that, an imbalance in the homeostasis of transition metals such as copper (Cu), zinc (Zn), and iron (Fe) also contributes to oxidative stress by promoting $OH^{\bullet}$ production from H_2O_2 via Fenton reaction with further damage to proteins and DNA[48][49][50][51][52]. Protein modification through nitrosylation, carbonylation, disulphide bond formation, and glutathionylation that resist degradation by forming cross-linked protein aggregates have been documented in early AD stages[53][54]. Elevated protein carbonyl (PC) levels, a marker of protein damage, have been identified both in AD and PD patients[55]. Moreover, the oxidative damage on DNA results in the formation of oxidized base adduct including 8-hydroxyguanine (8-OHG), 8-hydroxyadenine (8-OHA), and 5,6-diamino-5-formamidopyrimidine in both nuclear and mitochondrial DNA of the brain of patients with mild cognitive impairment (MCI), the earliest clinical manifestation of AD [56]. Despite the high capacity of ROS generation in the brain, the organ's defense mechanism against oxidative stress remains limited and reduced in ageing, due to low concentrations of endogenous antioxidants including CAT, GSH, GPX, and vitamin E compared to the liver[57][58][59][60][61][62]. The restricted regenerative capacity of postmitotic neuron cells has made oxidative stress more destructive to the brain, in which the lesion is permanent and accumulates over time compared to other organs[63][64].

2.3. Nutraceuticals as Free Radical Scavenger and Prevents Damage to Biomolecules

Nutraceuticals have been found to reduce free radicals by acting as a scavenger, hence preventing damage to lipid, protein, and DNA. There are many assays to measure the free radical scavenging activity of antioxidants. These assays measure the antioxidants ability to transfer a hydrogen atom (HAT) or donate an electron (ET) to free radicals, thus making them inactive. The commonly used assays include 1,1-diphenyl-2-picryhydrazyl (DPPH) assay, 2,2′-Azinobis (3-Ethylbenzothiazoline-6-Sulfonic Acid) (ABTS) assay, ferric ion reducing antioxidant power (FRAP) assay, total peroxyl radical-trapping antioxidant parameter (TRAP) assay, and oxygen radical absorbance capacity (ORAC)[65][66]. The nutraceuticals that carried out free radical scavenging activities will be further discussed in the following sections.

2.3.1. Resveratrol

Resveratrol or 3,5,4′-trihydroxy-stilbene that can be found in a wide variety of plants, including red grapes, berries, apples, plums, peanuts, tea, and red wine, is a naturally occurring polyphenol compound belonging to stilbenes group[67][68]. There are two types of resveratrol isoforms, the *cis*- and *trans*-resveratrol, in which the latter exhibits more beneficial effects compared to the former. Treatment with 10 mg/kg body weight (BW)/day of resveratrol for two weeks in the angiotensin II-induced early AD rats showed a significant reduction of $O_2^{\bullet-}$ in the nucleus tractus solitarius and hippocampus of the brain compared to untreated AD rats (Table 1)[69]. Similarly, piceatannol (trans-3,4,3,5 -tetrahydroxystilbene), which has a structure analogous to resveratrol with an added hydroxyl group at the 3′ of the benzene ring, exert neuroprotective effects in neurodegenerative diseases. Treatment with piceatannol in Aβ-induced cytotoxicity PC 12 cells, a cell line derived from pheochromocytoma of the rat adrenal medulla[70], markedly reduced the intracellular ROS generation, hence improving the cell viability[71]. The direct antioxidant ability of *trans*-resveratrol was demonstrated in the intracerebroventricular-streptozotocin (ICV-STZ) infused rats, an animal model for sporadic Alzheimer-type dementia. In this study, the MDA levels were markedly increased following disease induction, but were significantly reduced after continuous treatment with 10 mg/kg BW/day of resveratrol for 21 days[72]. The radical scavenging ability of resveratrol is thought to be contributed mostly by the 4′-hydroxyl group, as it is the most reactive compared to the 3- and 5-hydroxyl groups[73]. Resveratrol's ability to interact with hydroxyl and hydroperoxyl ($^{\bullet}OOH$) radicals by transferring a hydrogen in its phenol group can prevent further damage in oxidative stress[74].

2.3.2. Grape Seed Extract

Apart from resveratrol found in grapes, the grape seed also possesses health benefits, due to its proanthocyanidin content. Proanthocyanidins have been documented to have the potential as a dietary supplement in the management of neurodegenerative diseases. It has been shown to act as an in vivo radical scavenger that reduces oxidative DNA and protein damage[75]. Oral administration of 100 mg/kg BW/day of grape seed extract for 30 days in aged rats significantly reduced the 8-OHdG and DNA protein cross-links in the spinal cord, cerebral cortex, striatum, and hippocampus compared to controls (Table 1)[76]. Similarly, the oxidative mediated protein damage in aged rats could also be mitigated with grape seed extract supplementation[77]. The antioxidant capacity of grape seed extract is attributed by the phenolic compound, which acts as an in vivo radical scavenger, hence reducing oxidative DNA and protein damage[75].

2.3.3. *Ginkgo biloba* Extract

EGb 761 is a standardized herbal extract from the *Ginkgo biloba* plant that has demonstrated a neuroprotective ability. Administration of EGb 761 (100 µg/mL) to the transgenic neuronal cells secreting endogenous Aβ markedly reduced the level of ROS by 32% ($p < 0.05$) (Table 1)[29]. The EGb 761 is a potent antioxidant that can function in both aqueous solution (hydrophilic) and liposomes or a low-density lipoprotein (hydrophobic) environment[78]. Additionally, *Ginkgo biloba* extract has been shown to improve attention, memory, and cognition among human subjects in several randomized controlled trials[79][80].

2.3.4. Green Tea Polyphenols

Polyphenols found in green tea could also exert a productive radical scavenging activity. Examples of the green tea polyphenols include epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epicatechin (EC), which belongs to the flavanols group. Each of them has a different degree of lipid and hydroxyl radical scavenging abilities that is attributed to the ortho-3', 4'-dihydroxy moiety or an ortho-trihydroxyl group in their structures[81][82]. The neuroprotective effects of green tea have been demonstrated by Arab et al.[83]. In this interventional study, four pills amounting to 2 g of green tea/day in two divided doses were given daily for two months to 30 patients with severe AD. Each pill contained 50 mg of total polyphenols, including EGCG, EC, and ECG. At the end of the study, the total antioxidant capacity of plasma as measured by a FRAP assay was significantly improved as compared to baseline values (1140.7 ± 69.0 vs. 1391.1 ± 54.9, $p = 0.000$) (Table 1). Correspondingly, marked reduction in the levels of 8-OHdG (957.0 ± 52.5 to 719.7 ± 39.6 ng/mL, $p = 0.001$), MDA (4.3 ± 0.7 to 2.4 ± 0.3 nmol/mL, $p < 0.005$), and PC (1.9 ± 0.4 to 1.2±0.3 nmol/mg, $p < 0.05$) were observed as well[83].

2.3.5. Curcumin

Across Asia, turmeric is one of the main spices used in cooking. It is also routinely used in traditional Chinese and Indian medicine. It comes from a rhizomatous plant of the ginger family, known as Zingiberaceae. Turmeric extracts include curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which belong to the curcuminoid family. Curcumin, (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a turmeric polyphenol that causes yellow pigmentation. Its antioxidant capacity has been demonstrated by Frautschy et al.[84], where supplementation of 2000 parts per million (ppm) dietary curcumin for two months reduced brain IsoPs levels in the intracerebroventricular infusion of Aβ peptides in rats compared to Aβ treated rats on control diet (averaged value was 15 and 45 pg/mg, respectively; $p < 0.005$) (Table 1). Curcumin treatment at 500 ppm for six months was also shown to suppress LPO in the lumbar spine of Tg2576 APP transgenic mice that resulted in rescued motor function deficits compared to untreated transgenic Tg2576 APP mice (relative intensity of anti-HNE immunoreactivity level was 3.5 and 5.0, respectively; $p < 0.05$)[85]. Several studies have reported that the phenolic hydroxyl group in the curcumin structure is responsible for the inhibition of lipid peroxidation[86][87]. While curcumin has been shown to exert beneficial antioxidative effects against neurodegenerative disease, its efficacy is limited due to poor bioavailability, solubility, and structural stability[88]. Nevertheless, modification of curcumin by conjugating it with a carrier, encapsulation within the nanoparticle, and modification of its chemical structure have rendered positive results, including enhanced activity towards cancer cells, better wound healing properties, and strong antibacterial effects against *Pseudomonas aeruginosa* and *Staphylococcus aures*[89][90]. Shelat et al. [91] reported that treatment with oral CUR-CA-THIONE, an alternative formulation derived from curcumin using glutathione and casein as vectors for better water solubility and brain bioavailability[89], at a dose of 500 mg/kg BW/day for 15 days to the aluminum chloride ($AlCl_3$)-induced AD Wistar rats successfully inhibited LPO formation as measured by a thiobarbituric acid reactive substances (TBARS) assay ($p < 0.05$) compared to untreated AD rats, which was associated with improved locomotor and exploratory behavior. Moreover, in an in vitro study, a curcumin derivative, demethoxycurcumin, reduced intracellular ROS generation induced by neurotoxic rotenone[92].

2.3.6. Xanthorrhizol

Javanese turmeric or *Curcuma xanthorrhiza* Roxb. is another type of turmeric from the Zingiberaceae family that is commonly located on the island of Java, Indonesia and the neighboring Southeast Asian countries. Its bioactive compound includes Xanthorrhizol, which is a sesquiterpenoid extracted from the *Curcuma xanthorrhiza* Roxb. rhizomes. Xanthorrhizol (0.5, 1, 5, and 10 µM) showed an inhibitory effect on H_2O_2-induced lipid peroxidation in rat brain homogenate in a dose dependent manner, in which the highest dose reduced lipid peroxidation by 101.87 ± 1.62% of control ($p < 0.001$)[93]. Furthermore, 2 µM of Xanthorrhizol suppressed glutamate induced-ROS generation in the mouse hippocampal neuronal HT22 cells (130 vs. 210% of control, $p < 0.05$) that was comparable to that of curcumin (Table 1)[93].

2.3.7. Magnolol

Traditional Chinese and Japanese medicine have been using magnolol (5,5′-diallyl-2,2′-dihydroxy biphenyl), a bioactive polyphenolic compound isolated from the stem bark of *Magnolia officinalis*, for the management of a wide variety of diseases, including gastrointestinal and respiratory disturbances. Magnolol bark extract can also be found in chewing gum as prevention against plaques and dental caries. Previously, the beneficial effects of magnolol against neurodegenerative diseases have also been demonstrated. Supplementation of 30 mg/kg BW single dose of magnolol after induction of parkinsonism using 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) in mice exhibited a significant reduction in the thiobarbituric acid reactive substances (TBARS) level, an indicator of lipid peroxidation, compared to rats that received a vehicle solution (110 vs. 168% of control) ($p < 0.05$) (Table 1)[94]. In another study, extracts of *Magnolia cortex* at 1 mg/mL concentration reportedly exhibited the highest inhibitory effects on lipid peroxidation as measured by TBARS assay compared to other Kampo drugs (traditional Chinese/Japanese crude drugs) (73.15% vs. 0.00–62.55%)[95]. Further identification of this extract by high performance liquid chromatography (HPLC) revealed magnolol as one of the main phenolic constituents[95]. Likewise, the pre-treatment of magnolol (16 and 32 µM) in acrolein-induced oxidative damage in neuroblastoma cells markedly reduced the superoxide anions, LPO, and PC levels as opposed to the untreated acrolein-exposed cells[96].

2.3.8. Pycnogenol®

Pycnogenol is a patented name for the standardized extract exclusively from the bark of French maritime pine. It contains a mixture of a variety of bioflavonoids, including catechin, epicatechin, taxifolin, procyanidins, and phenolic acids[97]. Traditionally, the pine bark was used for the treatment of wounds and scurvy and has now progressed to be an effective nutritional supplement for various chronic diseases. Pycnogenol demonstrates an effective scavenging activity against oxygen free radicals and stable radicals. The pycnogenol quenching capacity towards DPPH radicals is proportional to Trolox[98] [98]. Pre-treatment of 100 µg/mL pycnogenol on acrolein-induced cytotoxicity in neuroblastoma cells significantly reduced ROS (190 vs. 470% of control), superoxide anions (150 vs. 260% of control), PC (140 vs. 190% of control), and 4-HNE bound proteins (130 vs. 200% of control) formation compared to untreated acrolein-exposed cells (all $p < 0.001$) (Table 1)[99]. In the hippocampus and cerebral cortex of ICV-STZ induce AD rats, pycnogenol pre-treatment at a dose of 10 mg/kg BW for three weeks remarkably reduced the PC content ($PC_{hippocampus}$: 35 vs. 45 nmol/mg; $PC_{cerebral\ cortex}$: 40 vs. 50 nmol/mg) and TBARS levels ($TBARS_{hippocampus}$: 2.0 vs. 3.0 nmol/mg; $TBARS_{cerebral\ cortex}$: 5.0 vs. 7.0 nmol/mg) in contrast to the untreated ICV-STZ rats, ultimately improved the cognitive performance (all $p < 0.05$)[100]. Antioxidant capacity of pycnogenol has also been demonstrated in a clinical trial. In this trial, 25 healthy individuals supplemented with 150 mg/day of pycnogenol for six weeks showed a 40% increase in the plasma ORAC against baseline values (3.5 vs. 2.5 µM Trolox equivalent, $p < 0.05$)[101] [101]. Furthermore, smokers who were prescribed with 50 mg of pycnogenol had lowered plasma reactive oxygen metabolites after two weeks by 25.3% from the baseline value (459.4 ± 65 vs. 342.2 ± 56 Carr units) compared to those receiving a placebo[102].

2.3.9. Guarana Seed Extract

Guarana seed is native to the South American continent, especially in the Amazon region, and are primarily consumed by the Brazilians as a dietary supplement and energy drink. It contains very high levels of caffeine as well as polyphenols such as catechins and epicatechins[103]. Recently, in vitro antioxidant assay done on a variety of Brazilian herb extracts, including from guarana seeds, have been reported[104]. Moreover, the antioxidant and anti-ageing potential of guarana seed, together with its protective effect on neurodegenerative diseases, has been well documented[103][105][106]. Guarana seed extract (100 and 1000 µg/mL) exerts significant antioxidant capacity as shown by a TRAP assay that was similar to 40 µg/mL of caffeine. In addition, there was a significant reduction of intracellular ROS production in acrolein-induced cytotoxicity on human neuronal-like cells to similar levels in control cells ($p < 0.0001$) (Table 1)[107]. Comparably, Boasquívis et al.[106] demonstrated that 5, 10, and 50 mg/mL of guarana hydroalcoholic extract (GHE), which contains 166.07 µg/mL of caffeine, 36.35 µg/mL of EC, 34.59 µg/mL of catechin, and 2.49 µg/mL of theobromine, has a similar DPPH radical scavenging property as 500 µM of Trolox, a water-soluble analogue of vitamin E. Moreover, either a dose of 10 or 50 mg/mL of GHE markedly reduced intracellular ROS levels in *C. elegans* models of AD compared to untreated control ($p < 0.05$) and eventually prolonged the worm's lifespan[106]. The antioxidant ability of guarana seed extract is due to the synergistic effect of polyphenol compounds together with its high caffeine content[105].

2.3.10. Vitamin E

Vitamin E is a lipid-soluble vitamin that is primarily found in vegetable oils such as palm, coconut, sunflower, soybean, and wheat germ oils[108]. There are two classes of vitamin E, namely tocopherols and tocotrienols. Each class has four isoforms comprising α-, β-, γ-, and δ- tocopherols as well as α-, β-, γ-, and δ- tocotrienols. They exhibited strong

antioxidative properties that resulted in health-promoting effects such as in attenuating osteoporosis, cardiovascular, and neurodegenerative diseases[109][110][111][112]. The direct antioxidative properties of vitamin E include its ability to donate hydrogen atom from its chromanol ring that neutralizes free radicals[113]. In this process, tocopherol and tocotrienol become oxidized to form stable tocopheroxyl- and tocotrienoxyl-radicals. Due to its lipid solubility, vitamin E is distributed mainly in the lipid membrane, which is crucial in terminating the lipid peroxidation chain reactions. These molecules can be converted back to their reduced states by interacting with other endogenous antioxidant systems to continue the scavenging process. Supplementation of tocotrienol rich fraction (TRF) (150 mg/day) for six months to healthy older adults significantly reduced MDA (0.14 vs. 0.22 nmol/mL) and DNA damage levels (95 vs. 125 arbitrary unit, AU) compared to their baseline values (both $p < 0.05$) (Table 1)[114]. Moreover, the administration of TRF (200 mg/kg BW) for eight months to healthy Wistar rats decreased DNA damage in comparison with control group (2.87 ± 0.48 vs. 5.96 ± 0.43%, $p < 0.05$), which was associated with improved cognitive function[115]. Similar results were also observed in APPswe/PS1dE9 mice, a transgenic AD mouse model that displays elevated Aβ plaque due to Swedish mutations in APP and deleted presenilin-1 in exon 9. Significant reduction of DNA damage (3.47 ± 0.35 vs. 14.04 ± 1.475%, $p < 0.05$) following supplementation with TRF at 200 mg/kg BW daily of for six months was observed compared to the unsupplemented control mice[116].

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