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EXPERT REVIEWS

Oxidative stress and Alzheimer's disease: dietary polyphenols as potential therapeutic agents

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Oxidative stress has been strongly implicated in the pathophysiology of neurodegenerative disorders such as Alzheimer's disease (AD). In recent years, antioxidants – especially those of dietary origin – have been suggested as possible agents useful for the prevention and treatment of AD. This article reviews the role of oxidative stress and the contribution of free radicals in the development of AD, and also discusses the use of antioxidants as a therapeutic strategy in the amelioration of this illness. The antioxidant potential of polyphenolic compounds obtained from dietary sources, such as anthocyanins from berries, catechins and theaflavins from tea, curcumin from turmeric, resveratrol from grapes and peanuts, the dihydrochalcones aspalathin and nothofagin from rooibos and the xanthone mangiferin from honeybush, are discussed in this review. The neuroprotective effects of these phytochemicals in preclinical models of AD are highlighted. Finally, innovative concepts, novel hypotheses, current challenges and future directions in the use of dietary polyphenols for the treatment of AD are discussed.

Keywords: β-amyloid • Alzheimer's disease • aspalathin • catechin • curcumin • dietary antioxidant • mangiferin • mitochondria • nothofagin • oxidative stress • polyphenol • resveratrol

Over the past two decades, the role of free radicals and their involvement in oxidative stress have been studied extensively in the pathophysiology of several age-related diseases, such as cancer, diabetes, cardiovascular and neurodegenerative diseases [1–4]. An increasing body of evidence suggests that oxidative stress due to excessive production of free radicals – both reactive oxygen species (ROS) and reactive nitrogen species (RNS) – play a major role in the pathogenesis of these diseases [5,6]. Antioxidant therapy for the treatment of several chronic diseases has been under investigation in recent years, with some reported success [7]. The involvement of oxidative stress and the potential therapeutic use of antioxidants have been extensively studied in several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (Lou Gehrig's disease), as well as stroke [7–9]. The potential therapeutic and neuroprotective effects of several antioxidant molecules in dietary sources, such as vitamin C, vitamin E, omega-3 fatty acids and selenium, have been investigated in both preclinical and clinical paradigms [1,10]. Polyphenolic compounds obtained from several natural sources exhibit potent antioxidant properties. Polyphenols such as catechins from green tea, curcumin from turmeric and resveratrol from grapes have shown significant antioxidant, anti-inflammatory and neuroprotective effects [11–19]. In this review, we highlight the role of oxidative stress in AD and evaluate the antioxidant and neuroprotective effects and the therapeutic potential of polyphenolic compounds obtained primarily from dietary sources. Challenges, limitations, innovative concepts and future directions in the development of this therapeutic strategy are also discussed.

Free radicals including ROS and RNS possess both beneficial and harmful roles in biology. Free radicals mediate receptor activation, gene expression, and are involved in several cellular signaling systems. Oxidative damage occurs when the excessive production of free radicals is not counteracted by the endogenous antioxidant mechanisms – a phenomenon termed 'oxidative stress'. At increased levels, free radicals damage membrane lipids, nucleic acids and both

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structural and functional proteins [2,20]. Oxidative stress can be defined as the imbalance between the production of free radicals and a biological system's ability to readily detoxify the reactive intermediates and repair the resulting damage [4]. Simply put, "it is a disturbance in the pro-oxidant–antioxidant balance in favor of the former, leading to oxidative damage" [21]. Although there is a basal level of oxidative damage to lipids, proteins and nucleic acids, there exists an essential antioxidant system that prevents the formation of free radicals, and also repairs and replaces oxidized biomolecules. The failure of this system produces oxidative injury and disease [22]. Endogenous antioxidant defense mechanisms primarily consist of enzymes such as superoxide dismutase, glutathione peroxidase and catalase, as well as nonenzymatic antioxidants such as vitamin C and vitamin E.

Reactive oxygen species, such as superoxide, hydroxyl, hydroperoxyl (protonated superoxide), and RNS, such as nitric oxide (NO) and peroxynitrite ($ONOO^-$), are the primary free radical species implicated in oxidative stress. Under normal physiological conditions, mitochondrial respiration and ATP synthesis represent the primary source of free radicals. ROS and RNS are generated as by-products of mitochondria-catalyzed reactions of the electron transport chain [23,24]. Cellular inflammation due to macrophage activation also produces a variety of free radicals, such as superoxide and NO [25]. The inducible form of the enzyme nitric oxide synthase (iNOS) is expressed as a result of microglial activation in response to stressful conditions, such as infection and trauma. Environmental pollutants, xenobiotics, toxins, metal-catalyzed reactions and ultraviolet irradiation trigger free radicals resulting in oxidative stress [3,26].

Oxidative stress due to increased production of free radicals results in oxidative damage to biomolecules, such as lipids, proteins and nucleic acids. Lipid peroxidation of the polyunsaturated fatty acid residues in cellular phospholipids produces malondialdehyde and 4-hydroxy-2-nonenal [27]. Oxidative damage to proteins, including enzymes, transporters and ion channels, involves loss of histidine residues, bityrosine crosslinks and introduction of carbonyl groups and formation of protein-centered alkyl, alkoyl and alkylperoxyl radicals that undergo peptide-bond cleavage. The side chains of all amino acid protein residues are susceptible to ROS-/RNS-mediated oxidative damage [28]. The rapid reaction of superoxide with NO results in formation of the highly reactive $ONOO^-$ species, which promotes nitrosation of cysteine sulfhydryl groups, as well as nitration of tyrosine and tryptophan residues. This irreversible nitration of tyrosine residues prevents the phosphorylation and adenylation of tyrosine residues of several regulatory proteins [3]. Oxidative stress affects the functioning of several transport proteins, such as Na^+/K^+-ATPase, resulting in increased intracellular Ca^{2+} levels, which in turn activates a panoply of proteolytic enzymes [29]. The hydroxyl radical reacts with all components of the DNA molecule and damages the purine and pyrimidine bases as well as the deoxyribose sugar. Both nuclear and mitochondrial DNA are susceptible to oxidative damage, although the latter is more vulnerable because mitochondrial DNA molecules lack nucleotide excision machinery and are not protected by histones [30].

Oxidative damage results not only from an increase in free radicals and subsequent oxidative stress but also from a failure of the antioxidant repair systems. Halliwell and Gutteridge define an antioxidant as "any substance that when present at low concentrations compared with those of an oxidizable substrate such as lipids, proteins and DNA, significantly delays or prevents oxidation of that substrate" [2,31]. This definition essentially highlights the importance of the damage to the target studied, and the source of reactive species used when the antioxidant action is examined. There is no universal 'perfect' antioxidant – the title essentially depends on the source, nature and severity of the oxidative insult. The use of antioxidants as a therapeutic strategy in both prevention and treatment of chronic diseases has been widely advocated [1,4,9,32]. Besides antioxidants, such as vitamin C and vitamin E, several synthetic compounds with potential antioxidant and free-radical quenching properties, such as the nitrone-based free radical trap α-phenyl-*tert*-butylnitrone, known as PBN, have been extensively studied as potential therapeutic agents. The pharmacological and potential therapeutic effects of these antioxidants have been examined in preclinical and clinical studies [32,33]. Several plant-derived compounds also possess potent antioxidant and free-radical scavenging properties. These natural antioxidants, many possessing polyphenolic, flavonoid, carotenoid and terpenoid structures, have demonstrated their usefulness in the prevention and treatment of several illnesses, such as cancer, diabetes, cardiovascular diseases and neurodegenerative disorders [1,10,19,34,35].

Oxidative stress & neurodegenerative diseases

A large body of evidence has accumulated over the past few years that strongly implicates free radical-induced oxidative damage in the pathogenesis of several neurodegenerative diseases, such as AD, PD, dementia and stroke [2,9,36–39]. Post-mortem studies in patients suffering from neurodegenerative diseases have shown increased levels of oxidative markers of lipid, protein and DNA damage [40]. Both ROS and RNS have been implicated in the etiology of degeneration [5,40]. The extremely high amount of oxygen and glucose consumption renders the brain especially sensitive to oxidative damage [41]. The CNS processes approximately 20% of basal oxygen consumption, although the brain constitutes only approximately 2% of total body weight. The brain is also extremely rich in more easily peroxidizable fatty acids and phospholipids and is also not particularly abundant in antioxidant enzymes. It has been shown that the brain has only 10% catalase activity compared with the liver. ROS production in the brain is essentially due to the mitochondrial respiratory chain, which is also the most abundant source of the superoxide anion. Other sources of neuronal ROS include mixed function oxidases, as well as several other oxidative processes, such as the oxidative deamination of catecholamines [42].

Besides ROS, RNS have also been implicated in the pathophysiology of neurodegenerative diseases. NO is a highly diffusible gas that plays an important role in neurophysiological processes. In the brain, endothelial and neuronal forms of nitric oxide synthase are essentially responsible for regulating NO production under normal physiological conditions. However, in response to stressful pathophysiological stimuli, such as infection, trauma

and neuronal injury, microglia and astrocytes become activated and secrete several mediators of inflammation, such as cytokines. This in turn leads to expression of iNOS, which results in massive NO production. NO reacts rapidly with superoxide to form $ONOO^-$, which is one of the most reactive RNS [43]. $ONOO^-$ reacts with several biological macromolecules, such as membrane lipids, enzymes, transporters and other proteins [44]. $ONOO^-$ has been shown to react with carbon dioxide forming an adduct that, upon subsequent decomposition, forms various other RNS [45].

Several neurochemical mechanisms have been proposed that address the involvement of oxidative stress in several neurodegenerative diseases. Mitochondrial dysfunction, resulting in impaired energy (ATP) production and increased free radical production, has been implicated as a significant mechanism of neurodegeneration. Thus, reduced activities of several mitochondrial processes, especially complex I, have been observed [46,47]. The role of mitochondrial respiration in free radical generation, oxidative stress and neurodegeneration has been critically reviewed by several researchers [48–51]. Neurochemical mechanisms of oxidative stress-induced neuronal damage in neurodegenerative diseases and the potential neurotherapeutic properties of antioxidants have been presented in several excellent reviews [2,4,5,20,32,52].

Oxidative stress, mitochondria, antioxidants & AD

Alzheimer's disease is the most common form of progressive dementia associated with the aging population. The already high incidence of this neurodegenerative disease is predicted to have a dramatic increase owing to an increasingly aging population in the world. It is estimated that the approximately 4 million cases of AD in the USA will rise to a staggering 13 million by 2050 [53,54]. In the past two decades, a significant amount of effort has been invested in preclinical and clinical paradigms to understand the etiology and pathophysiology of AD, with a view to producing effective therapeutic options. One of the most characteristic pathological findings in AD brain is the accumulation of amyloid-β (Aβ) peptide, derived from the amyloid precursor protein. AD also shows neurotransmitter deficiency, with the most characteristic observation being loss of cholinergic markers [55]. An overwhelming amount of evidence implicates oxidative stress in the pathophysiology and progression of AD. Formation of free radicals, both ROS and RNS, has been shown to contribute to the development of this disease [8,56–58]. Studies have found increased amounts of Fe^{3+} and Al^{3+} ions in the brain of AD patients, suggesting that redox processes play a catalytic role in the generation of free radicals [59]. Increased lipid peroxidation has been documented in AD, as evidenced by significantly increased malondialdehyde and 4-hydroxy-2-nonenal levels in multiple brain regions, as well as in the cerebrospinal fluid of AD patients compared with normal subjects [60,61]. Several studies have reported evidence for protein oxidation in AD. Protein carbonyl moieties are increased in several brains regions, such as frontal lobe and hippocampus, in AD subjects compared with age-matched controls. Another study found elevated levels of nitrotyrosine in AD brains [62,63]. Besides lipids and proteins, nucleic acids are also susceptible to oxidative damage in AD. Mecocci *et al.* showed an increase in 8-hydroxy-2-deoxyguanosine, a biomarker of both nuclear and mitochondrial DNA in AD subjects [64]. Studies on the amyloid precursor protein transgenic mouse model of AD have consistently shown elevated levels of markers of oxidative stress [65,66]. The presence of Aβ also increases the formation of free radicals and elevates markers of oxidative stress in numerous *in vitro* studies [67,68].

The role of mitochondria in the pathogenesis of AD has been extensively studied and neuronal mitochondrial damage has been suggested as the primary cause of AD [69]. AD subjects show significantly higher levels of damaged mitochondria than age-matched controls [70,71]. Mitochondrial respiration contributes to free radicals, and mitochondrial impairments have been observed and implicated in AD [49,56,70]. In these cases, damaged mitochondria are not able to maintain cellular energy demands, leading to increased free radical production, interruption of oxidative phosphorylation and, ultimately, decreased ATP levels [69]. Long and coworkers have reported that aged rats show decreased levels of endogenous antioxidants and decreased activities of mitochondrial complexes I, IV and V, and that this damage was restored by mitochondrial antioxidant therapy [72].

In AD, oxidative damage in the frontal cortex increases with the severity of the disease [73]. This increase in oxidative damage correlated with a decrease in cellular antioxidant defense mechanisms [73]. The increase with oxidative damage has been linked to defective oxidative phosphorylation in the mitochondria. These defects include reduced levels of complex IV activity (cytochrome C oxidase) [74,75] and reduced complex V activity [76], resulting in lower levels of ATP. In addition, Aβ may be directly linked to apoptosis. Evidence in differentiated neuronal SK-N-BE cells demonstrated that Aβ affected mitochondrial Bax, Bcl-2 and the release of cytochrome C, resulting in increased apoptosis (Figure 1) [77].

A considerable amount of effort has been invested in the past decade to examine the potential use of antioxidants as a therapeutic strategy in AD [1,4,52]. The pharmacological effects of several agents with antioxidant properties, such as acetyl-L-carnitine, β-carotene

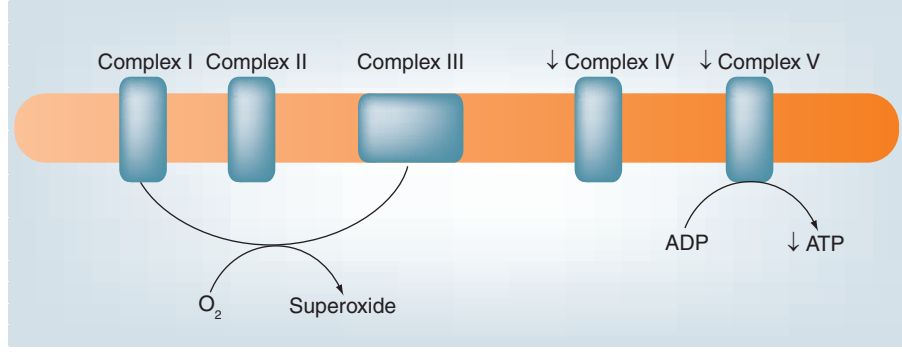

Figure 1. Mitochondrial respiration complexes associated with free radical production and reduced activity and/or expression.

from carrots, lipoic acid, omega-3 fatty acids obtained from fish oil and selenium, as well as vitamin C and vitamin E, are the focus of several preclinical and clinical studies in AD [78–80]. Several plant-derived products have received attention as potential therapeutics in AD. Most notable of these are the sesquiterpenic trilactone bilobalide and its biosynthetic precursor ginkgolide. Bilobalide is under investigation by several groups and is suspected to be a key agent that produces several of the reported neuroprotective effects of *Gingko biloba* extracts [81,82]. The aforementioned compounds fall outside of the scope of this review owing to their chemical structure type, and we will not detail their pharmacology further.

The therapeutic efficacy of vitamin E, the most studied antioxidant in AD, has been shown to be extremely disappointing. Only one study has shown vitamin E to be partially effective in AD and most studies have failed to observe any therapeutic or cognitive benefits due to vitamin E [83]. According to the conclusions of the *Cochrane Database* there is no evidence of the efficacy of vitamin E in the prevention or treatment of people with AD or mild cognitive impairment [84]. Some studies suggest that vitamin E treatment may even be detrimental in AD patients [85].

Components of vitamin E may have differential antioxidant effects in the AD brain. For example, 5-nitro-γ-tocopherol was shown to be significantly increased in AD brain [86]. When γ-tocopherol and α-tocopherol were evaluated for their ability to protect rat mitochondrial α-ketoglutarate dehydrogenase from peroxynitrite (generated by SIN-1), it was found that only γ-tocopherol afforded protection [86]. These data suggest that γ-tocopherol is a better scavenger of peroxynitrite and may account for its increased nitrated form in AD brain.

In recent years, several plant-derived molecules, mostly from dietary sources, with antioxidant properties, such as organosulfur compounds primarily obtained from garlic, soy isoflavones, lycopene from tomato, tea polyphenols and many other dietary agents, have shown promising neuroprotective effects in preclinical models of AD [19]. The potential therapeutic benefits of these dietary antioxidants in AD are currently under intense investigation across the globe [10,18]. Praticò provides an excellent summary of notable clinical studies that investigated the potential therapeutic benefits of antioxidant therapy in AD patients [57].

Dietary antioxidant polyphenols

Several epidemiological studies have highlighted the important role of fruits, vegetables, nuts and spices in the diet in lowering the risk of chronic illnesses, such as cancer and neurodegenerative diseases [87]. In recent years, several dietary agents have gained considerable attention as potential preventive and therapeutic agents for several serious maladies [88]. Almost three decades ago, the National Academy of Sciences recommended the daily consumption of five or more servings of fruits and vegetables daily in its 'Five-a-Day' program [89]. The therapeutic potential of dietary agents is due to the presence of several bioactive molecules with potent antioxidant properties [34,90]. The Food and Nutrition Board of the National Research Council in the USA has defined a dietary antioxidant as a substance in foods that significantly decreases and counteracts the adverse effects of free radicals, such as ROS and RNS, on normal physiological function in humans [91]. Dietary antioxidants come from diverse and wide-ranging sources; however, most possess several unsaturated alternate double bonds, hydroxyl groups and more than one phenolic group. The multiple hydroxyl groups present in polyphenolic molecules react with peroxides forming quinines and reducing the peroxide moiety. It has been suggested that it is the aforementioned structural properties that underlie the potent antioxidant and free radical quenching properties of these biomolecules [92]. Endogenous enzymatic and nonenzymatic antioxidants protect against ROS and RNS generated under normal physiological conditions. However, it is the exogenously administered antioxidants, under conditions of insult-induced excessive free radical production, that reduce the risk of tissue injury and consequential development of serious diseases in human populations [93].

The term polyphenols popularly refers to a diverse group of chemical substances found in the plant kingdom. More than 8000 compounds having more than one phenol moiety have been identified and divided into approximately ten different classes, such as curcuminoids, flavonoids, phenyl propanoids, stilbenes and lignans [94]. Polyphenols are secondary metabolites and are essential for plant defense against viral, bacterial and fungal infections. They also protect plants from abiotic processes, ultraviolet irradiation, ozone, temperature fluctuations, wounding and toxins [95]. Growing evidence regarding the health benefits of dietary products, such as fruits, vegetables, legumes, spices, honey, oils and popular beverages such as beer, wine and tea, can be attributed to polyphenols [96,97]. Polyphenolic compounds have been shown to be involved in apoptosis, gene transcription and signal transduction mechanisms, and also possess potent antioxidant properties. The aforementioned pharmacological effects afford polyphenols with preventive and therapeutic benefits in several chronic age-related illnesses [98,99]. Polyphenols have been examined for their potential therapeutic effects in neurodegenerative diseases, especially AD and PD [19,100].

A considerable amount of data, accrued in the past decade, has convincingly demonstrated the antioxidant, anti-amyloidogenic and neuroprotective effects of polyphenols in preclinical *in vivo* and *in vitro* models of AD. Anthocyanins obtained from berries; catechins and theaflavins – the tea polyphenols; curcumin obtained from turmeric; resveratrol present in peanuts, grapes and red wine; the dihydrochalcones aspalathin and nothofagin from rooibos; and mangiferin found in honeybush, are the most significant and important dietary polyphenols that have been investigated for their neuroprotective effects in paradigms related to the pathobiology underlying aging and AD [10–18,101–106]. Chemical structures of some major dietary polyphenols are depicted in Figure 2. The pharmacological effects of these polyphenols in models of oxidative stress in brain (presented in Table 1) strongly suggest that these polyphenols may also possess considerable potential as prophylactic and therapeutic agents in AD. A succinct review highlighting the botanical and geographical sources, chemical characteristics, epidemiological evidence and other highlights of these important phytochemicals is presented in the following sections.

Table 1. Effects of dietary polyphenols on pathogenic events linked to Alzheimer's disease.

Study	Antioxidant	Dietary source	Pharmacological effect	Ref.
Joseph *et al.* (2003)	Anthocyanidins Anthocyanins	Berries	Blueberry supplementation prevented deficits in Y-maze performance in *APP* + *PS1* transgenic mice	[152]
Joseph *et al.* (2004)		Bilberry (*Vaccinium myrtillus*)	Berry fruit extracts antagonized the amyloid-β-induced deficits in Ca^{2+} flux in M1-transfected COS-7 cells	[153]
Ramirez *et al.* (2005)		Blackberry (*Rubus fruticosus*)	Lyophilized blueberries and bilberries significantly enhanced short-term memory and improved working memory in the radial arm maze in adult rats	[154]
Zhu *et al.* (2008)		Blueberry (*Vaccinium spp.*)	Blueberry administered in diet prevented the amyloid-β-induced microglial activation via inhibition of p44/42 MAPK in mice	[155]
Hartman *et al.* (2006)	Anthocyanidins Anthocyanins Ellagic acid	Pomegranate (*Punica granatum*)	Pomegranate juice improved behavior and decreased amyloid-β load in a mouse model of AD	[156]
Lee *et al.* (2005)	Catechins Theaflavins	Tea – black, green (*Camellia sinensis*)	Green tea extract attenuated the amyloid-β (25–35)-induced cell death, ROS levels, 8-OHdG formation, p53, Bax and caspase-3 expression, and prevented the amyloid-β (25–35)-induced activations of the NF-κB and ERK and p38 MAPK pathways in PC12 cells	[157]
Rezai-Zadeh *et al.* (2005, 2008)			EGCG decreased the amyloid-β levels and plaques, suppressed sarkosyl-soluble phosphorylated tau isoforms and prevented the working memory and cognitive impairments in 'Swedish' mutant APP-overexpressing mice	[158,159]
Lu *et al.* (2006)			Green tea polyphenols ameliorated the deleterious effects of D-galactose and amyloid-β (25–35) in mice, and improved the animal's learning, memory, prolonged latency time and error numbers determined by using water maze and other tests	[160]
Bastianetto *et al.* (2006)			Green and black tea extracts inhibited amyloid-β aggregation and/or the formation of amyloid-β-derived diffusible neurotoxin ligands and also provided neuroprotection in primary cultures of rat hippocampal cells exposed to amyloid-β-derived peptides	[161]
Rasoolijazi *et al.* (2007)			EGCG administration protected against amyloid-β-induced memory and coordination impairment in male Wistar rats	[162]
Haque *et al.* (2008)			Green tea catechins prevented cognitive deficits, increased lipid peroxide levels and ROS species in Wistar rats infused with amyloid-β (1–40) into the cerebral ventricle	[163]
Ehrnhoefer *et al.* (2008)			EGCG inhibited the fibrillogenesis of both α-synuclein and amyloid-β by directly binding to the natively unfolded polypeptides and prevented their conversion into toxic, on-pathway aggregation intermediates	[164]

8-OHdG: 8-hydroxy-2'-deoxyguanosine; AChE: Acetylcholinesterase; AD: Alzheimer's disease; AIF: Apoptosis-inducing factor; APP: Amyloid precursor protein; EGCG: Epigallocathechin-3-gallate; GFAP: Glial fibrillary acidic protein; GSH: Glutathione; iNOS: Inducible nitric oxide synthase; LDH: Lactate dehydrogenase; LPS: Lipopolysaccharide; MDA: Malondialdehyde; PS: Presenilin; ROS: Reactive oxygen species; TBARS: Thiobarbituric acid reactive substances.

Table 1. Effects of dietary polyphenols on pathogenic events linked to Alzheimer's disease (cont.).

Study	Antioxidant	Dietary source	Pharmacological effect	Ref.
Kim *et al.* (2001)	Curcumin	Turmeric (*Curcuma longa*)	Curcumin, demethoxycurcumin and bisdemethoxycurcumin protected PC12 and normal human umbilical vein endothelial cells from amyloid-β (1–42) insult	[125]
Lim *et al.* (2001)			Curcumin significantly reduced the oxidized proteins, IL-1β, GFAP, insoluble and soluble amyloid-β and plaque burden in an AD transgenic mouse model	[165]
Ono *et al.* (2004)			Curcumin treatment inhibited accumulation of amyloid-β and amyloid-β fibril formation *in vitro*	[166]
Giri *et al.* (2004)			Curcumin inhibited amyloid-β-induced cytochemokine gene expression and CCR5-mediated chemotaxis of THP-1 monocytes by modulating early growth response-1 transcription factor	[167]
Yang *et al.* (2005)			Curcumin inhibited formation of amyloid-β oligomers and fibrils, binding to plaques and reduced amyloid-β burden in Tg2576 mice	[168]
Garcia-Alloza *et al.* (2007)			Curcumin disrupted existing plaques and partially restored distorted neurites in an AD mouse model	[129]
Park *et al.* (2008)			Pretreatment with curcumin significantly reversed the amyloid-β-induced oxidative stress, DNA damage, elevated intracellular calcium and tau phosphorylation	[169]
Pan *et al.* (2008)			Curcumin improved the learning and memory abilities in AD mice and inhibited the $AlCl_3$-induced apoptosis in PC12 cells	[170]
Thomas *et al.* (2009)			Curcumin reduced genomic instability events in a transgenic mouse model of AD	[171]
Inanami *et al.* (1995) McKay and Blumberg (2007)	Dihydrochalcones	Rooibos (*Aspalathus linearis*)	Chronic administration of rooibos extract containing the dihydrochalcones aspalathin and nothofagin, prevented age-related accumulation of lipid peroxides in several regions of rat brain as assessed by the TBARS assay and MRI	[103] [132]
Grzanna *et al.* (2004)	Gingerols Shogaols	Ginger (*Zingiber officinale*)	Ginger extract inhibited LPS-, cytokine- and amyloid-β-induced expression of the proinflammatory genes *TNF-α*, *IL-1b*, *COX-2*, *MIP-α*, *MCP-1* and *IP-10* in cultured TNP-1 monocytes	[172]

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Table 1. Effects of dietary polyphenols on pathogenic events linked to Alzheimer's disease (cont.).

Study	Antioxidant	Dietary source	Pharmacological effect	Ref.
Russo *et al.* (2003)	Resveratrol	Grapes (*Vitis vinifera*) Peanuts (*Arachis hypogaea*) Red wine	Black grape skin extract prevented the LDH release, ROS and MDA production, as well as DNA fragmentation induced by amyloid-β (25–35) or serum from AD patients in human vein endothelial cells	[173]
Conte *et al.* (2003)			Resveratrol treatment inhibited tyrosine kinase activity and significantly reduced the amyloid-β (1–41)-induced cytotoxicity in PC12 cells	[174]
Jang and Surh (2003)			Resveratrol attenuated amyloid-β-induced cytotoxicity, apoptotic features, intracellular ROS accumulation and transient NF-κB activation in PC12 cells	[175]
Savaskan *et al.* (2003)			Resveratrol attenuated amyloid-β and H_2O_2-induced cytotoxicity and enhanced the intracellular free-radical scavenger GSH in SH-SY5Y cells	[176]
Li *et al.* (2004)			Grape seed extract polyphenol attenuated amyloid-β-induced cytotoxicity, apoptosis, intracellular ROS accumulation and lipid peroxidation in PC12 cells	[177]
Han *et al.* (2004)			Pre-, co- and post-treatment with resveratrol significantly attenuated amyloid-β-induced cell death in a concentration-dependent manner in rat primary hippocampal cultured cells	[178]
Marambaud *et al.* (2005)			Resveratrol demonstrated a proteasome-dependent anti-amyloidogenic activity and markedly lowered the levels of secreted and intracellular amyloid-β produced from HEK293 cell line transfected with human APP	[179]
Kim *et al.* (2006)			Resveratrol prevented growth inhibition and inhibited iNOS and COX-2 expression in amyloid-β-treated C6 glioma cells	[180]
Wang *et al.* (2008)			Red wine significantly attenuated AD-type deterioration of spatial memory function and amyloid-β neuropathology in Tg2576 mice	[52]
Rivière *et al.* (2007)			Resveratrol effectively and dose-dependently inhibited amyloid-β polymerization *in vitro*	[181]
Wang *et al.* (2008)			Grape-derived polyphenolics prevented amyloid-β oligomerization and attenuated cognitive deterioration in a mouse model of AD	[182]
Karuppagounder *et al.* (2009)			Supplementation with resveratrol diminished plaque formation in the medial cortex, striatum and hypothalamus in a transgenic mice model of AD	[183]
Thomas *et al.* (2009)			Grape seed polyphenols reduced genomic instability events in a transgenic mouse model of AD	[171]

8-OHdG: 8-hydroxy-2'-deoxyguanosine; AChE: Acetylcholinesterase; AD: Alzheimer's disease; AIF: Apoptosis-inducing factor; APP: Amyloid precursor protein; EGCG: Epigallocathechin-3-gallate; GFAP: Glial fibrillary acidic protein; GSH: Glutathione; iNOS: Inducible nitric oxide synthase; LDH: Lactate dehydrogenase; LPS: Lipopolysaccharide; MDA: Malondialdehyde; PS: Presenilin; ROS: Reactive oxygen species; TBARS: Thiobarbituric acid reactive substances.

Table 1. Effects of dietary polyphenols on pathogenic events linked to Alzheimer's disease (cont.).

Study	Antioxidant	Dietary source	Pharmacological effect	Ref.
Sánchez *et al.* (2007)	Xanthones	Honeybush (*Cyclopia intermedia*)	In the mouse, the xanthone mangiferin protected against DNA fragmentation in brain and reduced lipid peroxidation in brain homogenates (39%)	[141]
Gottlieb *et al.* (2006)			Mangiferin was found to be neuroprotective in both *in vitro* and *in vivo* models of ischemia. *In vitro*, glutamate-induced neuronal cell death decreased in the presence of mangiferin through attenuated receptor-mediated calcium influx, oxidative stress and apoptosis. *In vivo* in rats, mangiferin – administered after the insult – diminished free radical generation and neuronal loss in the hippocampal CA1 region after transient forebrain ischemia, and improved functional metrics in behavioral tests	[104]
Jung *et al.* (2009)			Mangiferin significantly improved long-term cholinergic memory and ameliorated scopolamine-induced learning deficits in mice through AChE inhibition or cholinergic receptor stimulation and inhibition of NF-κB activation	[105]
Campos-Esparza *et al.* (2009)			Mangiferin reduced the formation of ROS, activated enzymatic antioxidant systems, and restored mitochondrial membrane potential while simultaneously inhibiting glutamate-induced activation of calpains to normalize levels of phosphorylated Akt kinase and Erk1/2 and cytosolic Bax, inhibited AIF release from mitochondria, and regulated the nuclear translocation of NF-κB	[106]

8-OHdG: 8-hydroxy-2′-deoxyguanosine; AChE: Acetylcholinesterase; AD: Alzheimer's disease; AIF: Apoptosis-inducing factor; APP: Amyloid precursor protein; EGCG: Epigallocathechin-3-gallate; GFAP: Glial fibrillary acidic protein; GSH: Glutathione; iNOS: Inducible nitric oxide synthase; LDH: Lactate dehydrogenase; LPS: Lipopolysaccharide; MDA: Malondialdehyde; PS: Presenilin; ROS: Reactive oxygen species; TBARS: Thiobarbituric acid reactive substances.

Anthocyanins

Anthocyanins, such as cyanidin, delphinidin, malvidin and petunidin, are a group of water soluble polyphenols responsible for the red, blue and purple colors and antioxidant property of berries. These water soluble, pigmented polyphenolic compounds occur in high concentrations in several popular berry fruits of *Vaccinium* as well as other genera, such as bilberry, blackberry, blueberry, cranberry, raspberry and strawberry, as well as cherries and currants. Significant levels of polyphenols have also been reported in a wide range of edible berries found all over the world, such as boysenberry, cloudberry, elderberry, huckleberry, lingonberry, mulberry and wineberry. Several epidemiological studies have highlighted the health benefits of anthocyanins in chronic illnesses, such as cancer, diabetes and neurodegenerative diseases [107–109]. The antioxidant and free radical quenching properties of anthocyanins have been highlighted in recent years [110]. A review of scientific as well as popular literature reveals that the anticancer effects of anthocyanins have been most studied in recent years. However, the neuroprotective and antioxidant effects of anthocyanins present in several dietary sources, such as blueberries, have been documented in several preclinical pathoetiological models of neurodegenerative diseases and are highlighted in Table 1. A recent study showed that tart cherry juice, a rich source of anthocyanins, protected healthy older men and women against forearm ischemia–reperfusion-induced oxidative damage, while also decreasing several markers of oxidative stress compared with a control group [111].

Another major source of anthocyanins is pomegranate (*Punica granatum*) – recently touted as a 'super fruit'. Pomegranate is an ancient fruit praised since biblical times for its curative properties. It has gained prominence in recent years as a potential therapeutic agent in several major illnesses and its antioxidant and therapeutic effects are under current investigation [112,113].

Catechins & theaflavins

Tea, made from the leaves of the *Camellia sinensis* plant, is, after water, the most widely consumed beverage in the world and especially popular in Asian cultures. White, green, oolong and black tea are obtained from the same botanical source and vary in degree of processing, namely drying and fermentation. Tea is a particularly rich source of polyphenolic compounds, known as catechins and theaflavins [16]. The degree of processing decreases the quantity of catechins and increases the theaflavin content. Hence, white and green teas have the highest levels of catechins, and theaflavins are mostly found present in black tea [114]. Several epidemiological studies suggest the regular consumption of tea as an important factor responsible for the lowered occurrence of several age-related diseases and longevity in several far eastern cultures, such as Japan. Tea polyphenols have been a subject of intense investigation to identify their potential therapeutic properties in various serious illnesses [115–116]. Of all the polyphenols present in tea, epigallocathechin-3-gallate, popularly known as EGCG, is the most widely used and studied tea polyphenol [12,15,17]. Catechins and theaflavins have been shown to possess significant antioxidant and neuroprotective effects in preclinical models of neurodegenerative diseases, especially AD

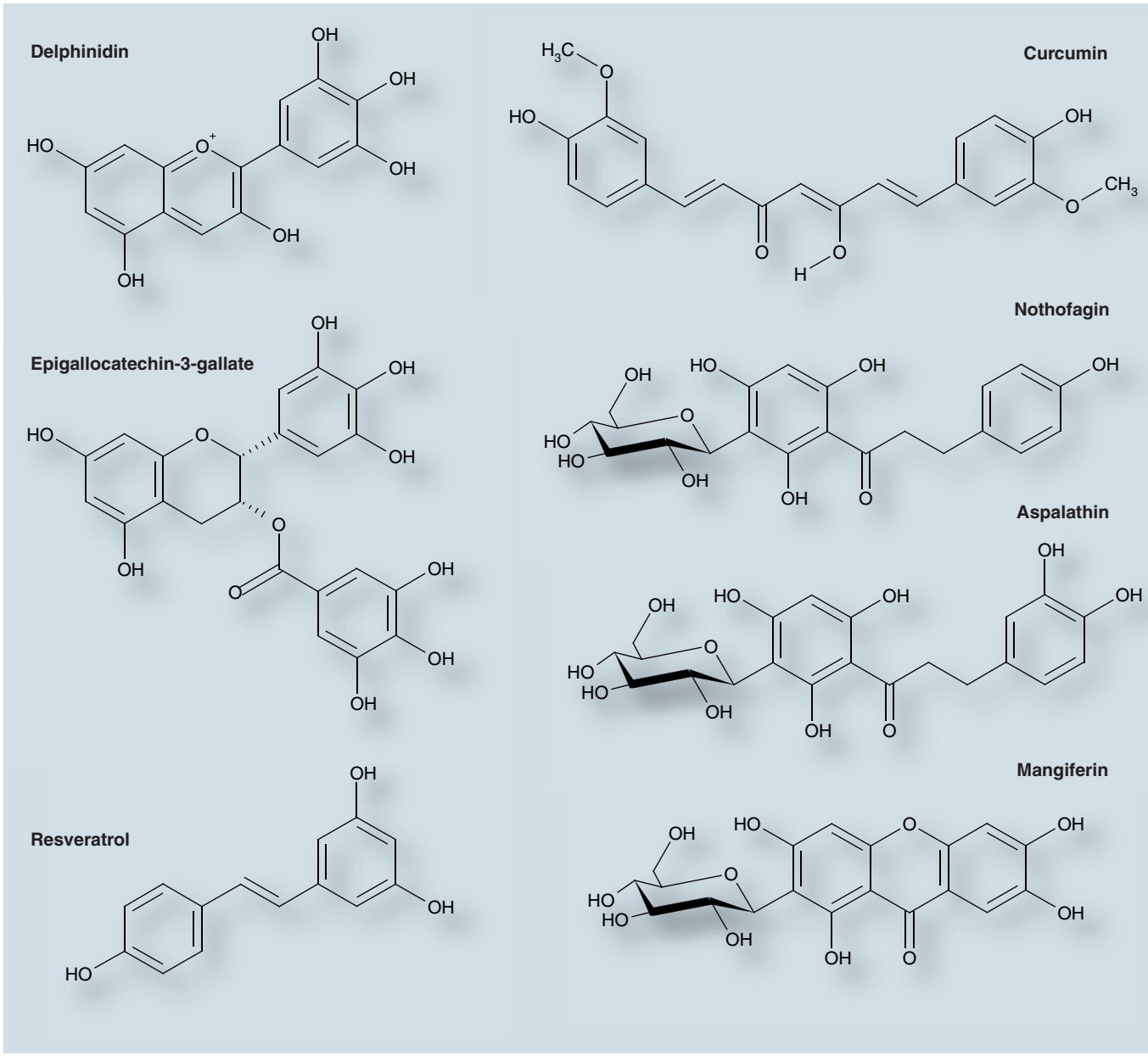

Figure 2. Dietary polyphenols.

and PD [10,11,19,117,118]. Tea polyphenols, especially EGCG, have consistently demonstrated their antioxidant potential against free radicals, such as superoxide anion, as well as iron-induced [12–14] and age-associated lipid peroxide accumulation in the brain [119]. Besides their antioxidant effects, tea polyphenols have also been shown to effect several cellular and molecular targets in signal transduction pathways associated with cell death and cell survival [11,16–18]. One of the important pharmacological effects that make tea polyphenols, especially EGCG, attractive candidates in the pharmacotherapy of AD, is the beneficial effects on age-related cognitive deficits and memory loss [120]. In a recent study, EGCG showed accumulation in mitochondria and displayed protective effects against mitochondrial oxidative stress in rat neurons, making it an attractive molecule for mitochondrial antioxidant therapy in AD [121].

Curcumin

Popularly known as Indian saffron, the curry spice turmeric contains intense yellow colored curcuminoid polyphenols, such as curcumin, desmethoxycurcumin and bis-desmethoxycurcumin. Turmeric (*Curcuma longa*) is a rhizome grown in tropical regions of South Asia. Curcuminoids possess significant antioxidant and anti-inflammatory properties and have shown therapeutic promise in autoimmune, cardiovascular, pulmonary, neoplastic and neurodegenerative diseases, as well as age-related maladies [122]. Curcumin is one of the most investigated molecules obtained from a dietary agent. It was almost a decade ago that epidemiological studies by Ganguli and coworkers suggested a link between reduced prevalence of AD in the Indian population with the consumption of turmeric in food [123]. Following this

observation several *in vivo* and *in vitro* studies have documented the neuroprotective effects of curcumin in preclinical models of AD and PD [18,124]. Curcumin showed protective effects greater than the classic antioxidant vitamin E against Aβ-induced toxicity in PC12 cells [125]. Although the free radical quenching property of curcumin has been firmly established, it shows several other pharmacological effects besides its antioxidant activity [126]. Curcumin has been shown to chelate redox-active metal ions, such as Cu^{2+} and Fe^{2+}, preventing metal-induced Aβ aggregation [127]. Curcumin treatment also upregulates Nrf-2 dependent genes that encode for several cytoprotective proteins and antioxidant enzymes [128]. Recently, Garcia-Alloza and coworkers showed that curcumin not only crosses the BBB but also binds to Aβ and accelerates its clearance rate [129]. Based on these findings, curcumin is considered as a therapeutic option in the treatment of AD [130,131].

Dihydrochalcones

Rooibos (*Aspalathus linearis*) is a member of the legume family of plants, and indigenous only to a small area in the western Cape of South Africa. Its dried and fermented leaves and twigs are used to make herbal tea that has been popular locally for generations and is now exported and consumed in many countries. The antioxidant activity of rooibos derives from flavonoids that include the dihydrochalcones aspalathin (2′,3,4,4′,6′-pentahydroxy-3′-C-β-d-glucopyranosyldihydrochalcone) and its structural analog nothofagin (differing only in that it lacks the A ring catechol group, see structures depicted elsewhere) [132]. Inanami *et al.* mounted a study to examine the effect of long-term (>20 months) administration of rooibos extract on lipid peroxidation in rat brain using the thiobarbituric acid reactive substances (TBARS) assay [103]. As alluded to earlier, increased lipid peroxidation is strongly associated with AD and aging in humans [60,61]. In the study by Inanami and coworkers [103], lipid peroxides were found to be significantly higher in the frontal and occipital cortex, the hippocampus and in cerebellum of control groups of 24-month-old animals compared with juveniles (aged 5 weeks). However, rats fed rooibos extract added to their diet *ad libitum* from the age of 3 months until they were sacrificed at 24 months had no significant elevation of markers for lipid peroxidation. Remarkably, in an additional MRI study by the same authors, the signal intensities for age-related markers in the frontal cortex, hippocampus and cerebellum of rooibos-treated rats mimicked those in 5-week-old rats, yet the same areas in untreated 24-month-old rats showed significant age and lipid peroxidation-related elevation of these markers. Thus, these authors conclude that their observations suggested that age-related accumulation of lipid peroxides in the brain, which was closely correlated with the morphological changes observed by MRI, reveal that chronic rooibos administration prevented age-related accumulation of lipid peroxides in several regions of rat brain [103].

Resveratrol

Resveratrol is a stilbene polyphenol present in several dietary and nondietary plant sources. It is found in significant amounts in berries, peanuts and grapes, as well as red wine [133,134]. It is a phytoalexin, its synthesis being induced by bacterial and fungal attack. Plants also produce resveratrol to counteract environmental stress, such as ultraviolet radiation and ozone exposure [135]. Resveratrol, the most widely studied molecule of dietary origin in recent years, gained significant prominence from the paradoxical observation made almost two decades ago that the French suffer a relatively low incidence of coronary heart disease, despite having a diet rich in saturated fats. It is believed that it is the moderate consumption of red wine (a rich source of resveratrol) that was responsible for this physiological phenomenon termed the 'French paradox' [136,137]. Resveratrol, a powerful antioxidant, has shown promise as a preventive as well as therapeutic agent in several inflammatory and oxidative stress-mediated illnesses, such as cardiovascular, neoplastic and neurodegenerative diseases [138,139]. Resveratrol shows pleiotropy in its pharmacological profile and, besides its prominent antioxidant effects, acts on multiple cellular targets [140]. The mechanisms implicated in the anticancer, cardioprotective and neuroprotective effects of resveratrol include, but are not limited to, inhibition of both synthesis and release of proinflammatory mediators, inhibition of inflammatory enzymes, such as iNOS and COX-2 and inhibition of the NF-κB signaling pathway [141]. Han and coworkers have reviewed the neuroprotective effects of resveratrol in several *in vitro* and *in vivo* models of neuronal injury, including AD and PD [142]. Resveratrol afforded protection against insult, attenuated oxidative injury and reversed cognitive deficits. Several studies in recent years have shown the neuroprotective and anti-amyloidogenic effects of resveratrol in both *in vivo* as well as *in vitro* models of AD, as presented in Table 1 and reviewed by several researchers [10,18,19]. Resveratrol has been shown to be permeable across the BBB [143] and also to scavenge free radicals in mitochondria [141], making it an extremely important molecule of choice for mitochondrial antioxidant therapy in AD.

Xanthones

A number of shrubs indigenous to the Cape Fynbos region of South Africa include the genus *Cyclopia*, the most common of these being *Cyclopia intermedia*, or the honeybush shrub. This species has been used for generations to produce honeybush herbal tea, which has been widely consumed in South Africa [132]. Several polyphenols, including the xanthones mangiferin and isomangiferin, as well as the flavanones hesperidin and eriocitrin, have been isolated from the honeybush. Of these compounds, mangiferin has been most widely studied in paradigms that relate to underlying pathophysiological mechanisms of AD. Sánchez *et al.* reported that mangiferin protected against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced oxidative damage in mouse brain [144]. In addition, mangiferin offered significant (22%) protection against DNA fragmentation in brain compared with TPA controls and reduced lipid peroxidation in brain homogenates by 39%. Work by Gottlieb *et al.* showed that neuronal cell death caused by glutamate in *in vitro* cell cultures was decreased in the presence of submicromolar concentrations of mangiferin [104]. In these cultures, receptor-mediated calcium influx was attenuated, oxidative stress was mitigated and a significant curtailment of apoptosis was measured. *In vivo*, mangiferin diminished the generation of measured free radicals due to transient forebrain ischemia, and

mitigated neuronal loss measured post-mortem in the hippocampal CA1 region in rats. Of importance is that mangiferin was administered after the insult [104]. Mangiferin may also improve long-term cholinergic-associated memory deficits, presumably by acetylcholinesterase inhibition or stimulation of cholinergic receptors, and inhibition of activation of NF-κB. In studies by Jung *et al.*, oral mangiferin significantly reversed scopolamine-induced passive avoidance test deficits in the mouse, improved escape latencies in training trials and improved performance in the Morris water maze test [105]. In addition, the xanthone also reduced acetylcholine and TNF-α levels induced by scopolamine in mouse brain, while simultaneously inhibiting NF-κB activation in microglial cells [105]. Studies by the group of Matute indicate that mangiferin reduces the formation of ROS and activates enzymatic antioxidant systems to restore the mitochondrial membrane potential [106]. Simultaneously, the compound inhibits glutamate-induced activation of calpains to normalize levels of phosphorylated Akt kinase and Erk1/2 and cytosolic Bax. Additionally, mangiferin was shown to inhibit apoptosis-inducing factor release from mitochondria, and regulated the nuclear translocation of NF-κB [106]. These combined results demonstrate that mangiferin exhibits promising antioxidant and antiapoptotic properties that may qualify the compound as a neuroprotecting agent in pathologies that involve excitotoxic neuronal death, including AD.

Expert commentary

The significant contribution of oxidative stress in the pathophysiology of AD highlights the critical role of the use of antioxidants as an important therapeutic strategy in the treatment of AD. The use of antioxidants from dietary agents remains a safe and effective treatment option that deserves serious attention. The virtual explosion of preclinical data in the past decade supports the neuroprotective properties of polyphenolic compounds, especially anthocyanins, catechins, curcumin, resveratrol, the dihydrochalcones aspalathin and nothofagin, and the xanthone mangiferin, as potentially important therapeutic agents for AD. However, a considerable amount of effort is required before the therapeutic potential of these polyphenols is realized.

The substantial literature of preclinical evidence highlighting the neuroprotective role of dietary polyphenols strongly suggests the need for translational research. Although the data are strongly suggestive of the therapeutic potential of these agents, only well-designed clinical trials can critically evaluate their therapeutic efficacy. It is important that measurement of selective clinical markers of oxidative stress be carried out along with the evaluation of the clinical end points. Furthermore, it should be kept in mind that the promising therapeutic effects of vitamin E against AD seen in preclinical studies could not be duplicated in several subsequent clinical trials [65,83]. Although dietary antioxidants as part of a daily diet are deemed safe, the issues of proper dose optimization and potential toxicity are also important considerations during clinical studies. Epidemiological studies that evaluate the possible relationship between regular consumption of dietary antioxidants as part of a normal diet, and the development of AD may also contribute to the assessment of the therapeutic potential of dietary antioxidants. Considering the critical role of mitochondrial dysfunction and oxidative stress, it is highly desirable to test these agents for mitochondrial antioxidant therapy in the treatment of AD.

Although several polyphenolic antioxidant molecules have shown considerable neuroprotective effects in rodent models of amyloid pathology, this has not been successfully translated in human paradigms. Dietary polyphenols, such as curcumin and green tea catechins, show extremely low bioavailability in humans and it has been suggested to be an important reason for the poor clinical trial outcomes [145]. It has also been suggested that the low brain concentrations achieved by the aforementioned agents may act in concert with the endogenous antioxidants in providing neuroprotection and may also be responsible for lack of toxicity of polyphenols, which is observed with other administered antioxidants.

Bioavailability and drug delivery are other areas that require development. A careful consideration of these aspects is particularly critical due to reported concerns about the poor bioavailability of polyphenolic antioxidants [146]. It is especially important to determine whether these agents are permeable to the BBB. Recently, the use of novel drug delivery systems has been suggested to improve bioavailability of dietary polyphenols. Formulations consisting of colloids, micelles, nanoparticles, cyclodextrin complexes and lipid microparticles have been evaluated with some early success [147–149].

Preclinical studies evaluating the pharmacological effects of dietary polyphenols utilized both the pure chemical compounds, such as curcumin, resveratrol and mangiferin, as well as botanical extracts, such as green tea extract, pomegranate juice, grape skin extract and rooibos extract. It becomes difficult to interpret the results of studies that utilize botanical extracts since they contain a mixture of dietary antioxidants and other components, the relative concentrations of which may vary depending upon the source and method of preparation of these extracts. Therefore, chemical characterization of such extracts is of critical importance. It has been suggested that several dietary antioxidants may be therapeutically more effective when used in combination rather than in single pure form. Many studies reveal that several compounds of dietary origin, effective in combination, were found to be ineffective when used in isolation [150]; thus, biochemical mechanisms that form the basis of this synergistic activity require systematic elucidation.

In conclusion, dietary polyphenols are powerful antioxidants that have pleiotropic effects and show considerable promise as safe and effective agents in the treatment of AD. Nevertheless, a significant amount of work and systematic efforts are required before the therapeutic potential of these agents can be realized.

Five-year view

Preclinical studies evaluating the neuroprotective effects of dietary polyphenols is expected to increase significantly in the next few years. It is also expected that preclinical data will lead to several clinical trials in selected population cohorts to examine the therapeutic efficacy, safety and bioavailability of these agents. In recent years, the use of natural products and nutritional

supplements for the prevention and mitigation of chronic illnesses has generated tremendous enthusiasm more among the population and less so among clinicians. However, several polls suggest that, within the next decade, the medical community is expected to become more receptive to the use of natural products in healthcare [151]. The use of natural products and dietary supplements is essentially unregulated and most products are freely available over-the-counter. Several problems arise with the use of these over-the-counter formulations, including product quality issues, interference with ongoing therapy and herb–drug interactions, which may lead to serious problems. It is expected that these issues will be addressed by both lawmakers and healthcare professionals in the coming decade.

Alzheimer's disease is a chronic disease and potentially requires long-term antioxidant therapy, either as a preventive strategy or as ameliorative treatment. In the next few years, it is expected that the safety issues of chronic use of dietary antioxidant compounds will be critically examined. Polyphenolic compounds owe their antioxidant activity and therapeutic potential to certain structural characteristics, such as multiple phenolic groups, unsaturated double bonds and hydroxyl moieties. Hence, it is expected that these phytochemicals will serve as lead compounds for the synthesis of semisynthetic analogs with better bioavailability. Most phytochemicals investigated for their therapeutic potential are obtained from fruits, vegetables, nuts and spices. It has been suggested that it is not only the phytochemicals obtained from the dietary sources detailed in the current review, but also the consumption of other dietary agents contained in the plant sources themselves that hold the key to the prevention and treatment of serious chronic illness. The role of nutrition in AD is currently under intense investigation and is expected to be examined even more critically in the coming years.

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Key issues

- Oxidative stress due to both reactive oxygen species and reactive nitrogen species plays an important role in the pathophysiology of Alzheimer's disease (AD).
- Antioxidant therapy has been investigated in the treatment of AD with some measure of success.
- Several phytochemicals obtained from dietary sources possess potent antioxidant properties and are under investigation as potential therapeutic agents for AD.
- Dietary polyphenols, such as anthocyanins from berries, catechins from green tea, curcumin from turmeric, resveratrol from grapes, aspalathin and nothofagin from rooibos, and mangiferin from honeybush, have been evaluated as potential preventive and therapeutic agents in AD.
- Dietary polyphenols have shown antioxidant, anti-inflammatory and neuroprotective effects in both *in vitro* and *in vivo* preclinical models of AD.
- A critical need exists to evaluate the therapeutic potential of dietary polyphenols in well-designed epidemiological studies and clinical trials.
- Several issues pertaining to the use of natural products, such as bioavailability, dose optimization, site-specific drug delivery, safety, synergy and use of novel dosage forms, are currently under investigation.
- Natural products and dietary supplements are currently not well regulated and mostly sold as over-the-counter products, resulting in improper use, drug–herb interactions and adverse effects. Better legislation and monitoring are required to properly utilize the therapeutic potential of dietary antioxidants.
- Dietary polyphenols are safe and effective antioxidants and their use as potential therapeutic agents in the treatment of AD merits serious investigation.
- The role of nutrition in the prevention and development of AD needs to be systematically elucidated.

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