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Nutritional approaches to combat oxidative stress in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) brains are characterized by extensive oxidative stress. Additionally, large depositions of amyloid β-peptide (Aβ) are observed, and many researchers opine that Aβ is central to the pathogenesis of AD. Our laboratory combined these two observations in a comprehensive model for neurodegeneration in AD brains centered around Aβ-induced oxidative stress. Given the oxidative stress in AD and its potentially important role in neurodegeneration, considerable research has been conducted on the use of antioxidants to slow or reverse the pathology and course of AD. One source of antioxidants is the diet. This review examines the literature of the effects of endogenous and exogenous, nutritionally-derived antioxidants in relation to AD. In particular, studies of glutathione and other SH-containing antioxidants, vitamins, and polyphenolic compounds and their use in AD and modulation of Aβ-induced oxidative stress and neurotoxicity are reviewed.

Keywords: Alzheimer's disease; Antioxidants; Glutathione; Polyphenols; Vitamins; Oxidative stress; Amyloid beta-peptide; Cellular response genes

1. Introduction

Alzheimer's disease (AD), the major dementing disorder of the elderly, has millions of victims worldwide. Amyloid β-peptide (Aβ), a 40–42 amino acid peptide, accumulates in the AD brain, and many researchers now believe that this peptide is central to the pathogenesis of this disorder [1]. In addition, the AD brain is under intense oxidative stress that is manifested by lipid peroxidation, free radical formation, protein oxidation, nitrotyrosine, advanced glycation end-products, and DNA/RNA oxidation [2–5]. Our laboratory has united these two observations into the Aβ-associated free radical oxidative stress model for neurodegeneration in AD brain [3,6,7]. Aβ in mechanisms that likely involve the single methionine at residue 35 [7–11], causes protein oxidation, lipid peroxidation, free radical formation, DNA oxidation, and neuronal cell death, in ways that are inhibited by free radical antioxidants [3–5,12–15]. In particular, the antioxidants vitamin E, melatonin, epigallocatechin gallate, N-acetylcysteine, α-lipoic acid, various flavones, estrogen and phytoestrogen, and polyphenols, such as curcumin, Ginkgo baloba extract, etc., among others, are protective against amyloid β-peptide-induced oxidative stress and neurotoxicity or oxidative modification produced by lipid peroxidation products caused by Aβ [12,13,17–28]. Aβ-induced oxidative stress and neurotoxicity has recently been reviewed [3–5].

The brain is particularly vulnerable to oxidative damage due to the high utilization of inspired oxygen, the large amount of easily oxidizable polyunsaturated fatty acids, the abundance of redox-active transition metal ions, and the relative dearth of antioxidant defense systems. Free radicals are produced from a number of sources, among which are enzymatic, mitochondrial, and redox metal ion-derived sources [29]. Aging, the major risk factor for AD [30], leads to loss of free radical scavenging ability by endogenous mechanisms [29]. Hence, the normal balance between free

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Table 1
Some Nutritional Sources for Antioxidant Nutrients

Natural compound	Food or beverage
Vitamin A	Meat, tomatoes, carrots, spinach
Vitamin B_1, B_{12}	Meat, beans
Vitamin C	Oranges, grapefruit, kiwi, mango, cabbage, tomatoes, brussel sprouts, broccoli, sweet potatoes
Vitamin E	Sunflower, peanut, walnut, sesame and olive oil
Carotenoids	Tomatoes, carrots, spinach
Ferulic acid	Tomatoes
Lipoic acid	Any meat
Anthocyanins	Blueberries, red wine
Epigallocatechin gallate	Green tea
Resveratrol	Red wine, grapes
Curcumin	Tumeric
Whey proteins	Cottage cheese

radical generation and free radical scavenging is disrupted with aging and other oxidative stress conditions [31].

Since oxidative stress may underlie some, if not all, aspects of AD neurodegeneration, and since Aβ appears central to the disease [3], considerable research has been aimed at reducing the effects of oxidative stress by use of free radical scavengers. Among the latter are those derived from nutritional sources, and it is this work that is the subject of this review.

2. Nutritionally derived antioxidants

There are two general classes of antioxidants, endogenous and exogenous. Among the former are the tripeptide glutathione (GSH), various vitamins, and products of reactions catalyzed by enzymes that are upregulated in response to oxidative stress, e.g., bilirubin from heme oxygenase and products of antioxidant response elements (ARE) [32] (see below). Among the exogenous, nutritionally derived antioxidants are different classes of molecules: those moieties that increase endogenous GSH levels or otherwise have reactive SH functionalities; vitamins; and phenolic and polyphenolic compounds [33,34] (Table 1).

2.1. Glutathione and other SH-containing antioxidants

The tri-peptide glutathione (γ-glutamyl-cysteinyl-glycine) is an endogenous antioxidant of great importance. Glutathione (GSH) is required for the maintenance of the thiol redox status of the cell, protection against oxidative damage, detoxification of endogenous and exogenous reactive metals and electrophiles, storage and transport of cysteine, as well as for protein and DNA synthesis, cell cycle regulation and cell differentiation [35]. Glutathione and glutathione-related enzymes play a key role in protecting the cell against the effects of reactive oxygen species. The key functional element of glutathione is the cysteinyl moiety, which provides the reactive thiol group. Glutathione is the predominant defense against reactive oxygen species (ROS), which are reduced by GSH in the presence of GSH peroxidase. As a result, GSH is oxidized to GSSG, which in turn is rapidly reduced back to GSH by GSSG reductase at the expense of NADPH. The thiol-disulfide redox cycle also aids in maintaining reduced protein and enzyme thiols. Without a process to reduce protein disulfides, vulnerable cysteinyl residues of essential enzymes might remain oxidized, leading to changes in catalytic activity.

Glutathione also aids in the storage and transfer of cysteine as well. Cysteine autoxidizes rapidly into cystine producing toxic oxygen radicals. To avoid the toxicity of cystine, most of the nonprotein cysteine is stored in glutathione.

In addition to protection against ROS, glutathione is an excellent scavenger of lipid peroxidation products such as HNE and acrolein, both of which have been found to bind proteins inhibiting their activities. Glutathione also reacts with saturated carbon atoms (epoxides), unsaturated carbon atoms (quinones, esters), and aromatic carbon atoms (aryl nitro compounds). This detoxification involves nucleophilic attack by GSH on an electrophilic carbon. This reaction can occur spontaneously, but most often is catalyzed by glutathione S-transferase.

Glutathione also forms metal complexes via nonenzymatic reactions. GSH functions in the storage, mobilization and delivery of metal ions between ligands, in the transport of metal across cell membranes, as a source of cysteine for metal binding, and as a reductant in redox reactions involving metals [35]. The sulfhydryl group of the cysteine moiety of GSH has a high affinity for metal ions such as mercury, silver, cadmium, arsenic, lead, gold, zinc, and copper, forming a thermodynamically stable complex that can be eliminated from the body.

Glutathione reacts with radicals as shown in Fig. 1A. Thus, means of increasing glutathione may prove beneficial against oxidative stress. For example, our laboratory has shown that elevated *in-vivo* glutathione protects brain membranes against oxidative stress associated with hydroxyl free radicals, peroxynitrite, and reactive aldehydic products of lipid peroxidation [4-hydroxy-2-nonenal (HNE) or 2-propenal (acrolein)] [20,21,36,37]. HNE and acrolein are increased in AD brain [38,39], and HNE is covalently bound in excess to the glutamate transporter in AD [40]. The latter finding, that could also be induced by addition of Aβ to synaptosomes [40], coupled with the reported loss of glutamine synthetase activity in AD brain [41], suggests that glutamate-stimulated excitotoxic mechanisms could be important in neurodegeneration in AD.

2.2. Vitamins

Vitamin levels and aging and dementia have been critically studied (Table 2). Nutrition has been related to aging, disease and cognitive decline. Youdim and Joseph reviewed

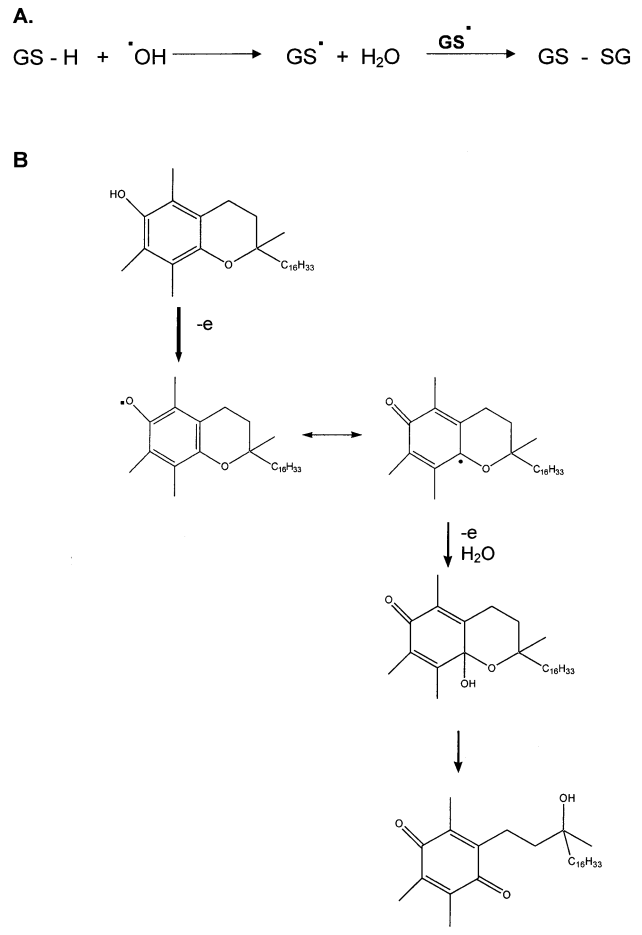

Fig. 1. (A). Scavenging of free radicals by glutathione to form oxidized glutathione. (B). Trapping of free radicals by vitamin E.

Table 2
Relative vitamin levels in aging and dementia

Reference	Study Population	Method	Results
[204]	AD	Plasma	Decreased Vit. E, retinol
[136]	AD Vascular dementia (VaD) PD with dementia (PDm)	Plasma	Decreased Vit. A in AD, VaD Vit. C in AD, VaD, PDm Vit. E in AD, VaD
[205]	AD	Plasma	Decreased Vit. A, E, C
[206]	AD, VaD	Plasma	Decreased Vit. A, E, β-carotene in AD Decreased Vit. E, β-carotene in VaD
[207]	AD	Serum	No change α-carotene, Decreased Vit. A, β-carotene
[135]	AD	Plasma	Decreased Vit. C
[208]	AD, VaD	Plasma	Decreased Vit. C, E Increased β-carotene in VaD
[209]	AD, dementia	Plasma	Decreased Thiamine
[210]	AD	Cerebrospinal fluid	Decreased Vit. B_{12}

studies reporting correlations among dietary carotenoids, vitamin E, and vitamin C and cognitive decline in aging [34]. The review of nine different studies had varying results. Most researchers showed no association with nutritional changes and increased dementia. Nourhashemi et al. [42] reviewed seven studies on the relationship between vitamin status and cognitive skills in elderly patients, revealing a correlation between low vitamin C, vitamin B_{12}, riboflavin, folic acid, niacin, thiamine, β-carotene, vitamin B_6 levels and decreased performance on cognitive tests.

An increase in these vitamins also showed a correlation with improved cognitive performance. Chandra investigated whether an optimum intake of all essential micronutrients would improve cognitive function in the elderly [43]. Healthy elderly where given a cocktail of vitamins and trace elements (vitamins A, E, C, D, B_{12}, B_6, β-carotene, thiamine, riboflavin, niacin, folate, iron, zinc, copper, selenium, iodine, calcium, and magnesium). The supplemented group showed a significant improvement in all cognitive tests except long-term memory recall. Thus, some studies show that nutritional deficiencies may be a contributing factor in the decline of cognitive function in old age and dementia.

Vitamin E, a phenolic compound, acts as an antioxidant by scavenging free radicals via the phenolic H-atom as shown in Fig. 1B. As discussed below, these reactions of vitamin E, vitamin C, and glutathione may be linked by various recycling pathways, thereby increasing efficency of these moieties against oxidative stress.

As noted, in AD there is evidence of subclinical deficiency in levels of vitamim E, C, folate, and GSH. Hence, dietary sources of these and other molecules that inhibit oxidative stress may be an important approach in delaying progression of and treating AD.

2.3. Polyphenols

Polyphenols are natural substances ubiquitously present in fruits and vegetables, as well as, beverages obtained from plants such as tea, red wine and olive oil. Flavonoids compose the largest group of polyphenols. Their skeletal structure consists of an aromatic ring condensed to a heterocyclic ring, attached to a second aromatic ring. Flavonoids are mainly divided into: anthocyanins, glycosylated derivative of anthocyanidin, present in colorful flowers and fruits, and anthoxantins, colorless compounds further divided in several categories including flavones, flavans, flavonols, flavanols, and isoflavones (Fig. 2). The remarkable antioxidant activity of these compounds is conferred by the numerous phenolic hydroxyl groups on the aromatic ring. The rapid

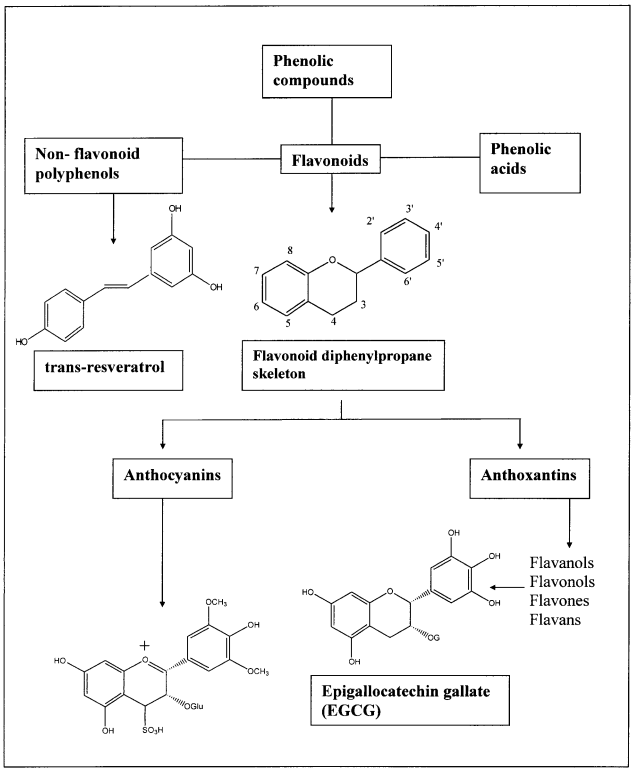

Fig. 2. Classification of natural polyphenols.

donation of a hydrogen atom to lipid peroxyl radical results in the formation of the polyphenol phenoxyl radical (PP$^{\cdot}$) according to the reaction

$$ROO^{\cdot} + PPH \rightarrow ROOH + PP^{\cdot}$$

that can be stabilized by further donation of another hydrogen or by reacting with another radical. In addition, flavonoids present efficient iron chelating activity, for which the 3-OH is important [44].

The physiological effects of flavonoids are particularly significant in those pathologies where the oxidative stress hypothesis is accepted and supported by experimental data, such as AD. *In vitro*, flavonoids are capable of scavenging superoxide anions [45] and hydroxyl radicals [46].

Once ingested, these compounds are capable of elevating the redox and antioxidant level [47]. In red blood cells, polyphenols enhance cell resistance to oxidative insult [48], as well as inhibit LDL oxidation in plasma [49]. The importance of these molecules in protecting cells from oxidative stress goes beyond the simple radical oxygen species (ROS) scavenging properties. In a recent study on neuronal cells [50], three different mechanisms of protection have been identified: Flavonoids can prevent cell death after glutamate injury by scavenging radicals, maintaining the correct glutathione levels and inhibiting Ca^{2+} influx, which represents the last step in the cell death cascade. These properties, together with anti-inflammatory properties attributed to some polyphenols [51], renders this class of compounds suitable for application where oxidative stress, together with inflammation and antioxidant defense depletion take place, such as AD.

2.4. Heme oxygenase as a target for cytoprotective strategies

Many approaches have been undertaken to understand AD, but the heterogeneity of the etiologic factors makes it difficult to define the clinically most important factor determining the onset and progression of the disease [52]. However, there is increasing evidence that factors such as oxidative stress and disturbed protein metabolism and their interaction in a vicious cycle are central to AD pathogenesis [3,32]. The pathology of Alzheimer's diseased brain, including amyloid plaques, neurofibrillary tangles and neuronal degeneration, indicates that neurons affected by AD exist under conditions of stress. In fact, the brains of AD patients undergo many changes classically associated with the heat shock response, which is one form of a stress response. These changes include reduced protein synthesis, disrupted cytoskeleton, increased number of proteins associated with ubiquitin, and induction of heat shock proteins which, in AD, is a primary event caused by protein conformational changes [53]. Heat-shock proteins are proteins serving as molecular chaperones, involved in the protection of cells from various forms of stress [32,54,55]. Recently, the involvement of the heme oxygenase (HO) pathway in antidegenerative mechanisms operating in AD has received considerable attention, as it has been demonstrated that the expression of HO is closely related to that of amyloid precursor protein (APP) [56]. HO induction, which occurs together with the induction of other HSPs during various pathophysiological conditions [57,58], by generating the vasoactive molecule carbon monoxide and the potent antioxidant bilirubin, could represent a protective system potentially active against brain oxidative injury [59].

Moreover, studies of *postmortem* brain tissue from Alzheimer's diseased patients have demonstrated increased NFκB activity [60]. This is a critical activator of genes involved in the cellular response to genotoxic insults, such as the response of human cells to DNA damage following ultraviolet light irradiation, the inducible nitric oxide synthase [61], cyclo-oxygenase (COX-2) which catalyzes the synthesis of proinflammatory prostaglandins, cytokine receptors, cell adhesion molecules, as well as important steps in the process of tumor promotion, or the progression of viral infections, such as the enhancement of HIV-1 transcription [62]. Evidence also indicates that Aβ peptide can induce NFκB activation in cultured neurons, and a strong correlation has been reported between increased NFκB activation and cycloxygenase-2 gene transcription in superior temporal lobe gyrus of Alzheimer's patients.

Given the broad cytoprotective properties of the heat shock response there is now strong interest in discovering and developing pharmacological agents capable of inducing the heat shock response. The therapeutic goal for these types

of agents is the safe induction of the heat shock response as a means to reduce organ pathology in diverse clinical conditions, such as ischemia-reperfusion, sepsis, and neurodegenerative insult. Notably, recent reports have demonstrated important interactions between the heat shock response and NFκB pathway [63]. For example, induction of heat shock response by thermal or nonthermal stimuli inhibited activation of the NFκB pathway in various *in vitro* and *in vivo* models [64]. Additionally, some pharmacological inhibitors of NFκB, each having distinct mechanism of inhibition, are able to induce the heat shock response [65].

These evidences, together with the findings that Aβ causes oxidative damage to and neurotoxicity of neurons [3,7], vitamin E blocks these effects in vitro [12,13,66,67], the glutamate transporter, Glt-1, is oxidatively modified in AD brain with increased opportunity for excitotoxic mechanisms to lead to oxidative stress and neurodegeneration [40], all indicate that excess formation of free radicals exists in AD brain [3]. Consequently, such free radicals may be influenced by antioxidants, which can thus modify the intensity of inflammatory reactions and degenerative damage.

Spices and herbs often contain phenolic substances with potent antioxidative and chemopreventive properties [68]. Spices form an important class of food adjuncts and are used to enhance the sensory quality of food. Recent studies show that some of the biochemical effects of spices are due to their active principles. Turmeric (*Curcuma longa* Linn, family: *Zingiberacee*) has been used as a coloring agent and food additive in Indian culinary preparations from time immemorial [69].

The active antioxidant principle in *Curcuma longa* has been identified as curcumin (diferuloyl methane). It is generally assumed that the phenol moiety is responsible for antioxidant properties of any plant phenolic compound. Consequently, the free radical chemistry of curcumin (an *o*-methoxyphenol derivative) has focused on its phenol ring [70]. The possible involvement of the β-diketone moiety in the antioxidant action of curcumin has been considered [71] and, as recently shown [72], the H-atom donation from the β-diketone moiety to a lipid alkyl or a lipid peroxyl radical has been reported as the potentially more important mechanism underlying its antioxidant action (Fig. 3a–d). In the case of H-atom donation to a bis-allylic radical, such as linoleic acid radical, the resulting product is a resonance-stabilized β-oxo-alkyl curcumin radical (Fig. 3b) with unpaired electron density distributed between three carbon and two oxygen atoms. This undergoes molecular reorganization, i.e., rapid intramolecular H-shift (Fig. 3c) generating the phenoxyl radical (Fig. 3d). When this molecular reorganization is not possible, as in trimethylcurcumin, or less efficient as in demetoxycurcumin and bisdemethoxycurcumin, these latter present with curcumin in natural extracts of Curcuma Longa, the β-oxo-alkyl radical adds oxygen at the central C atom to generate potentially damaging peroxyl radical.

Similar to the well-known synergism between lipid soluble vitamin E and water soluble ascorbate, it has been postulated [72] that the curcumin radical generated by an-

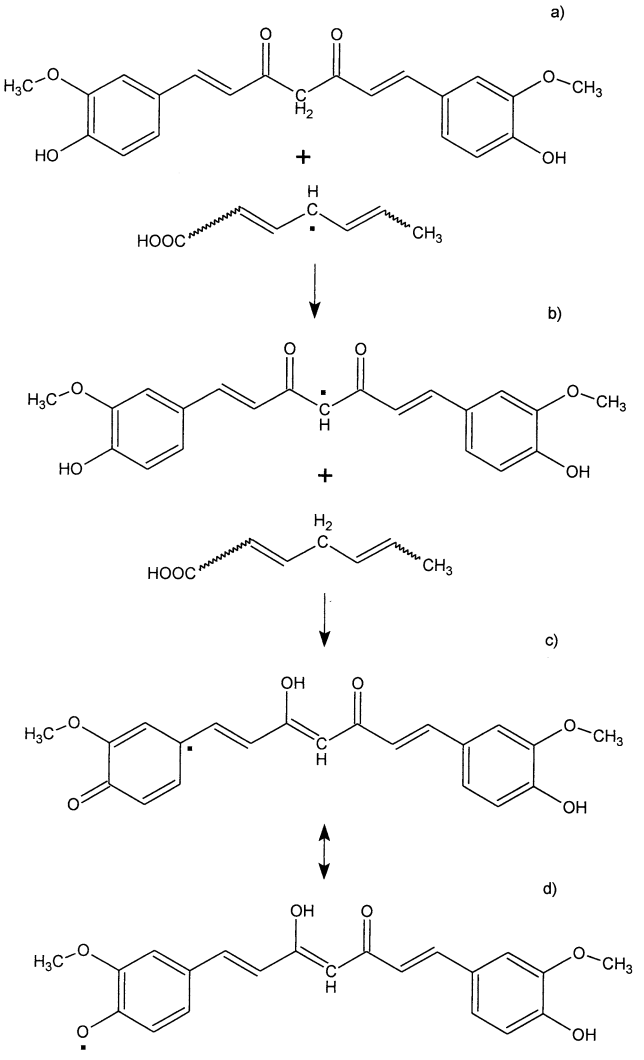

Fig. 3. Proposed mechanism for the antioxidant action of curcumin molecule.

tioxidant action might position itself at the border of the cell membrane adjacent to the acqueous milieu, in short "pops out" of the membrane to be repaired by water soluble antioxidant, such as catechins or ascorbate. Curcumin, as a powerful lipid soluble antioxidant, positions itself within the cell membrane, where it intercepts lipid radicals and becomes a phenoxyl radical. Being more polar than curcumin, phenoxyl radical travels to the membrane surface. Owing to the high reduction potential of phenoxyl curcumin radical (0.8 V, at physiological pH 7), this allows the curcumin intermediate to be easily repaired by electron donors with favorable oxidation potential, such as epigallocatechin gallate (0.43 V), catechin (0.55 V), or vitamin C (0.28 V). Such electron and associated proton transfer reaction will maintain optimal concentrations of curcumin at expense of water soluble antioxidants, in spite of its fast turnover and low physiological uptake. Moreover, curcumin free radicals can also react with each other or with other free radicals forming, either stable products such as curcumin dimers,

vanilin and ferulic acid [73] or, through a peroxyl linkage at the 3′ position of the curcumin phenolic ring, coupling products which generate, via intramolecular Diels-Alder reaction, non radical stable compounds [74].

Curcumin contains two electrophilic α,β-unsaturated carbonyl groups, which can react with nucleophiles such as glutathione [75]. By virtue of its Michael reaction acceptor function and its electrophilic characteristics, curcumin and several other polyphenolic compunds have been recently demonstrated to induce the activities of Phase I and Phase II detox system [76,77], e.g., inhibition of COX-1 and COX-2 enzymes [78] and stimulation of glutathione-S-transferase [79]. In addition to its ability to scavenge carcinogenic free radicals [71,80], curcumin also interferes with cell growth through inhibition of protein kinases. Although the exact mechanisms by which curcumin promotes these effects remains to be elucidated, the antioxidant properties of this yellow pigment appear to be an essential component underlying its pleiotropic biological activities. Of particular interest is the ability of curcumin to inhibit lipid peroxidation and effectively to intercept and neutralize ROS (superoxide, peroxyl, hydroxyl radicals) [81] and NO-based free radicals (nitric oxide and peroxynitrite) [82]. In this regard, curcumin has been demonstrated to be several times more potent than vitamin E [83].

The hydroxycinnamate, ferulic acid, is found in many fruits and vegetables such as the tomato [84]. Tomato consumption has been demonstrated to result in absorption and excretion of ferulic acid by humans [85]. Ferulic acid has been demonstrated to have antioxidant activity against peroxynitrite [86] and against lipid peroxidation [87–89]. Recently, we demonstrated that ferulic acid was protective against protein oxidation and lipid peroxidation in synaptosomal membranes, and against cell death and protein carbonyl formation in neuronal cell culture induced by the peroxyl radical initiator AAPH [90]. Ferulic acid possesses strong antioxidant capability because of resonance-stabilizing structural motifs on the benzene ring which could stabilize a phenoxyl radical [90]. The 3-methoxy and 4-hydroxyl electron donating groups stabilize the phenoxyl radical [90,91]. Additionally, the carboxylic acid group with an adjacent unsaturated carbon-carbon double bond stabilizes the radical with resonance, contributes another site for free radical attack, and may act by providing some lipid-solubility allowing protection against lipid-peroxidation [90]. Ferulic acid has been shown to be protective against *in-vitro* oxidative stress, absorbed and excreted by humans, and may be a promising candidate for therapeutic intervention in AD.

3. Studies of nutritionally-derived antioxidants in AD

3.1. SH-containing antioxidants

3.1.1. Whey proteins

Whey proteins consist of α-lactoalbumin, β-lactoglobulin, immunoglobulin, serum albumin and other unidentified proteins from pasteurized cow's milk. Whey proteins have demonstrated antioxidant activity [92–97]. Possible antioxidant mechanisms of whey proteins include free radical scavenging by amino acids such as tyrosine and cysteine [96–98] and chelation of transition metals by lactoferrin [99] and serum albumin [100], common whey proteins.

Ostdal [96] found that β-lactoglobulin is able to inactivate pro-oxidative heme proteins leading to the formation of dityrosine, the cross-linked oxidation product of two tyrosines, in β-lactoglobulin. This suggested that whey proteins are able to scavenge free radicals. Tong and co-workers [101] demonstrated that the high molecular weight (HMW) fraction of whey is able to inhibit lipid peroxidation and lipid peroxide formation through sulfhydryl groups in the proteins. These researchers also established that the HMW whey fraction is able to chelate iron, supporting possible antioxidant mechanisms.

Whey proteins are reported to increase levels of glutathione. Glutathione and glutathione enzymes play a key role in protecting cells against the effects of reactive oxygen species (ROS). In addition to direct scavenging of ROS, glutathione is an excellent trap for reactive products of lipid peroxidation, such as HNE and acrolein, both of which can inhibit enzyme activity after covalent binding to the protein [20,21]. Rats, on a diet in which the protein consisted only of whey proteins or β-lactoglobulin, had a 40% increase in reduced glutathione in the liver [102]. Mice fed the whey protein diets at 84 weeks of age exhibited increased longevity and increased liver and heart glutathione levels as compared to mice fed Purina mouse chow [103]. HIV patients taking a daily dose of 45 g of whey proteins for two weeks also had an increase in plasma concentration of glutathione [104]. β-lactoglobulin, serum albumin and lactoferrin are rich sources of cysteine and glutamylcysteine [105], thus providing the precursors for the synthesis of glutathione.

3.1.2. Lipoic acid

α-lipoic acid (LA) is a low molecular weight dithiol antioxidant that is an important co-factor in multienzyme complexes in the mitochondria. LA is readily available from the diet, absorbed through the gut and easily passes through the blood-brain barrier. In addition, LA is synthesized in the mitochondria [106]. As an antioxidant, LA and its reduced form, dihydrolipoic acid (DHLA) are capable of quenching reactive oxygen and nitrogen species such as hydroxyl radicals, peroxyl radicals, superoxide, hypochlorous acid and peroxynitrite and chelating metals such as Cd^{2+}, Fe^{3+}, Cu^{2+}, and Zn^{2+} [107]. LA also interacts with other antioxidants such as glutathione, ubiquinol, thioredoxin, vitamin C, and indirectly with vitamin E [108], regenerating them to their reduced forms. Several studies have demonstrated that LA and dihydrolipoic acid (DHLA), administered to cells and to mice, intraperitoneally (i.p.) increase glutathione levels [109]. The increase of glutathione is attributed to DHLA causing reduction of cystine, providing free cysteine to be taken up by the cell for the synthesis of

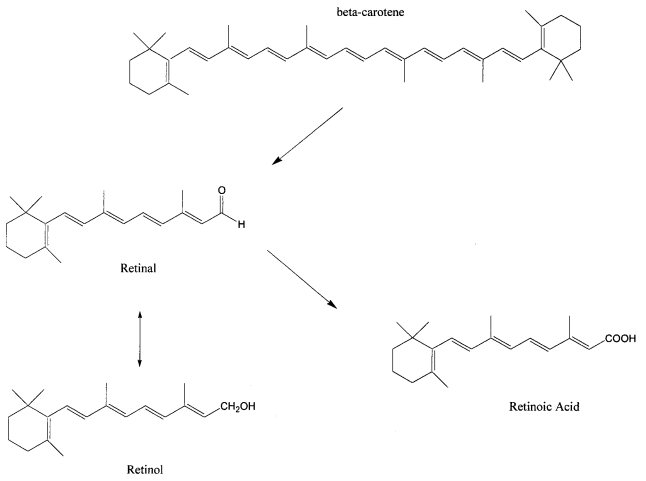

Fig. 4. Formation of retinoids from β-carotenes.

glutathione. Improved behavior and diminished markers of oxidative stress were reported for aged rats fed a diet supplemented with LA [110–112]. Recently, α-lipoic acid was administered to AD patients [113]. The non-randomized study gave 600 mg of lipoic acid daily for 337 days to AD and other dementia patients. The treatment led to a stabilization of cognitive functions in the study group as demonstrated by constant scores in two neuropsychological tests (mini-mental state examination: MMSE and AD assessment scale, cognitive subscale: ADAScog).

3.2. Vitamins

3.2.1. Vitamin A and carotenoids

Vitamin A or retinol is fat-soluble and can be absorbed in the diet from animal sources or synthesized from β-carotene from plant sources (Fig. 4). Vitamin A has many different roles in the body including vision, stimulating growth and differentiation of tissues, RNA synthesis, and as a sugar carrier. In the AD brain, the ability to synthesize retinoic acid was investigated, and increased retinal synthesis was found [114]. Retinalehyde dehydrogenase (RLDH), the enzyme that forms retinoic acid from retinaldehyde, was present in the hippocampus, frontal cortex, and parietal cortex. The RLDH activity of the hippocampus and parietal cortex was 1.5 to 2-fold higher in AD brain compared to controls. There was no difference in RLDH activity in the frontal cortex compared to controls [114].

The mobilization of retinol from storage in the liver is carefully regulated. A specific retinol-binding protein, RBP, binds all-trans-retinol, and is secreted into the plasma to be delivered to peripheral tissues. The protein profile of amyloid-enriched extracts from Alzheimer brain tissue was studied by enzyme immunoassay. The results demonstrated a significant increase of retinol-binding protein in amyloid enriched Alzheimer brain extracts compared to controls [115]. This finding suggests high demand for retinol by neurons that have high concentrations of amyloid deposition.

Dietary carotenoids, bioavailable from fruits and vegetables, have been implicated in biological processes relevant to human health and chronic disease. It is widely accepted that carotenoids from commercial preparations are more bioavailable than from fruits or vegetables and are less available from raw fruits and vegetables than from processed fruits and vegetables [116]. Some carotenoids such as β-carotene, α-carotene and β-cryptoxanthin are precursors of vitamin A. Central cleavage of β-carotene produces two molecules of retinol or vitamin A (Fig. 4). In addition to acting as precursors for vitamin A, carotenoids have antioxidant properties of their own. The antioxidant activity of carotenoids is largely due to the extended system of conjugated double bonds. Carotenoids can be efficient quenchers of singlet oxygen species and can directly scavenge free radicals.

3.2.2. Vitamin B_{12}

Vitamin B_{12} is not synthesized by animals or plants. Only a few species of bacteria synthesize this complex vitamin. Sufficient amounts of B_{12} can easily be acquired from meat. Vitamin B_{12} is converted in the body into two coenzymes: 5′-deoxyadenosylcobalamin and methylcobalamin. The B_{12} coenzymes participate in three types of reactions: intramolecular rearrangements, reductions of ribonucleotides to deoxyribonucleotides, and methyl group transfers. Cobalamin or vitamin B_{12} was administered to patients with cobalamin deficiency and dementia with additional symptoms of delirium [117]. Patients who showed mild to moderate dementia improved clinically. In contrast, patients who were severely demented showed no obvious clincial improvement. It was concluded that symptoms which probably indicated superimposed delirium such as clouding of consciousness, disorientation and clinical fluctuation, responded to the vitamin B_{12} supplementation, while the underlying dementia condition remained unchanged. Nilsson [118] also investigated the effect of cobalamin and folate supplementation on the cognitive function of elderly patients with dementia. Patients with mild to moderate dementia cognitively improved, as assesssed by increased MMSE test scores after vitamin supplementation, while severely demented patients did not improve clinically.

3.2.3. Thiamine or vitamin B_1

Thiamine or vitamin B_1 is important in the metabolism and the release of acetylcholine (Ach) from the presynaptic neuron. Synthesis of Ach is catalyzed by cholineacetyltransferase (ChAT), whose activity is deceased in AD brains [119]. HNE is bound to ChAT to a level greater than control after interaction with Aβ (1–42) [5], raising the possibility that lipid peroxidation induced by Aβ (1–24) causes the inactivation of ChAT in AD brains.

Thiamine deficiency is thought to be detrimental to the cholinergic system, and thiamine-dependent enzymes are

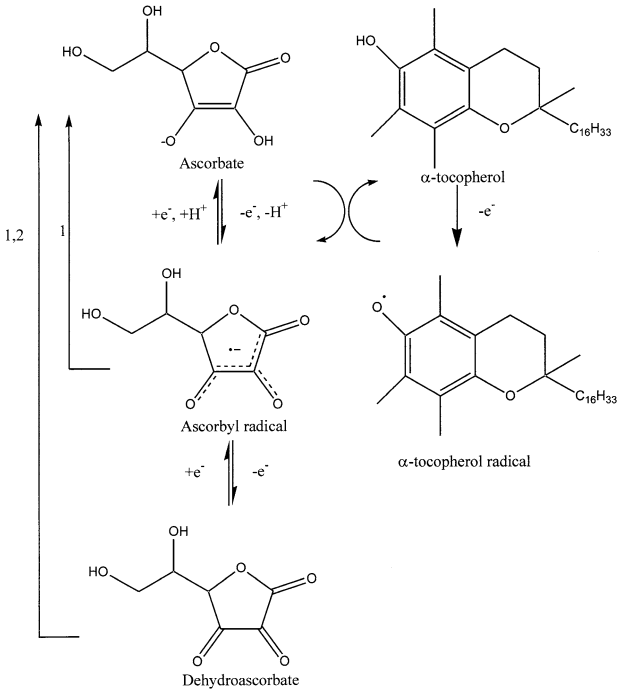

Fig. 5. Recycling of α-tocopherol radical by vitamin C. 1) thioredoxin reductase 2) GSH or NADPH dependent dehydroascorbate reduction enzymes.

altered in Alzheimer's disease [120]. Several studies have been done to determine the effects of thiamine supplementation on Alzheimer's disease with varying results. Blass et al. [121] noted a significant improvement in cognitive ratings in AD patients who took 3 g per day of oral thiamine for three months. Nolan and collegues saw no difference in mini-mental state scores after twelve months of 3 g per day oral thiamine in AD patients [122]. In contrast, Meador et al. [123] noted mild beneficial effect in dementia of Alzheimer patients after 3 to 8 g/day of thiamine was administered orally. A derivative of thiamine, fursultiamine was taken by AD patients, at an oral dose of 100 mg/day for twelve weeks. Mildly impaired Alzheimer's patients showed cognitive improvement [124]. Thiamine supplementation, possibly through its involvement with cholinergic neurons, may have possible therapeutic implications for AD.

3.2.4. Vitamin C

Humans lack the enzyme L-gulono-γ-lactone oxidase which is necessary for biosynthesis of vitamin C, ascorbate, and therefore must obtain ascorbate from dietary sources. Ascorbate is a water-soluble antioxidant present primarily as a monovalent anion at physiological pH. Ascorbate functions as an antioxidant by giving up to two electrons. Ascorbate can lose one electron to form the semidehydroascorbate, the ascorbyl radical, a relatively stable resonance-stabilized radical of low reactivity [125] (Fig. 5). The loss of a second electron results in the formation of dehydroascorbate. Ascorbate and ascorbyl radical have low reduction potentials putting these species on the lower end of the "pecking order" and they can therefore react with stronger oxidizing species such as hydroxyl radical, superoxide, etc. [126].

Ascorbate plays an important role with the lipophilic antioxidant vitamin E in protecting the membrane from oxidative stress. Ascorbate soluble in the aqueous phase can regenerate vitamin E which is present in the membrane. Ascorbate can reduce the tocopheryl radical, formed when vitamin E scavenges a lipid radical within the membrane. The hydroxyl group of vitamin E has been shown to be at the membrane-water interface, in close proximity to the water-soluble ascorbate [126] (Fig. 6). The tocopherol radical formed from the lipid radical can then be recycled back to tocopherol by ascorbate.

An important aspect of the antioxidant capability of ascorbate is the ability of oxidized ascorbate to be recycled back to the reduced ascorbate. Glutathione is important in the recycling of ascorbate by direct chemical reduction [127] and by glutathione-dependent enzymes [128,129]. Recently, dehydroascorbate reductase activity has been found to be present in brain cytosol and the enzyme was found to be present in several brain regions including the cerebellum and hippocampus [130]. This enzyme uses glutathione as an electron donor to restore ascorbate to a reduced state from dehydroascorbate [130]. Other enzymes that function to reduce dehydroascorbate to ascorbate are the NADPH-dependent enzymes 3α-hydroxysteroid dehydrogenase [129] and thioredoxin reductase [131]. Additionally, thioredoxin reductase has been shown to reduce the ascorbyl radical to ascorbate [132].

However, an important aspect of ascorbate chemistry is the pro-oxidant behavior of ascorbate *in vitro.* Ascorbate has long been known to participate in Fenton chemistry by reducing Fe(III) or Cu(II), yielding Fe(II) or Cu(I) and the ascorbyl radical. Fe(II) or Cu(I) can then catalyze the Fenton reaction with H_2O_2, resulting in production of hydroxyl radical [133]. Consequently, one must consider the possibility that long-term megadoses of vitamin C may cause oxidation in a living system.

Plasma ascorbate levels have been found to be decreased in AD patients as compared to control patients, in levels corresponding to dementia [134–136]. More interestingly, CSF levels of ascorbate were found to be decreased in AD patients as compared to control subjects which may hinder the reduction of tocopheryl radical back to tocopherol [137]. The synergistic vitamins C and E were chosen in a study in which 400 IU vitamin E and 1000 mg vitamin C were given daily to AD patients [138]. The combination of vitamin E and C increased vitamin E and C levels in plasma and CSF, making CSF and plasma lipoproteins less susceptible to *in vitro* oxidation. The plasma and CSF of patients given only vitamin E were not protected against *in vitro* oxidation. This study highlights the importance of the synergism between

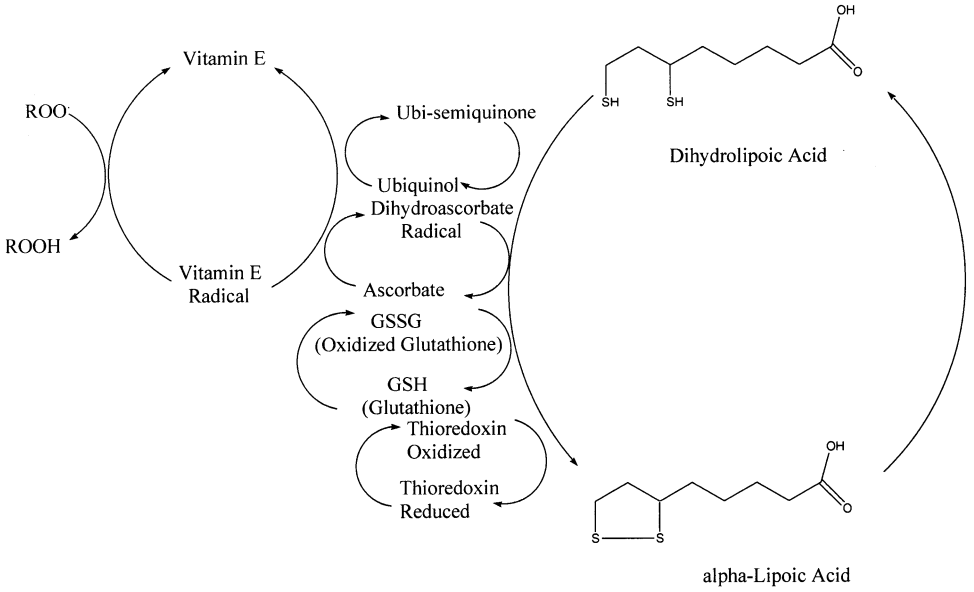

Fig. 6. Role of vitamin C, GSH, and lipoic acid as antioxidants.

vitamin E and C, suggesting that vitamin C should be given concurrently with vitamin E in AD patients.

3.2.5. Vitamin E

In neuronal cultures, the lipophilic antioxidant vitamin E inhibits Aβ-induced lipid peroxidation, protein oxidation, free radical formation, and cell death [12,13,16,67,139]. Lowered levels of vitamin E are observed in AD cerebrospinal fluid (CSF), a finding that was inversely correlated with levels of lipid peroxidation [140]. This latter observation is consistent with the increased lipid peroxidation reported for AD [2,3] and caused by Aβ [40,141].

Vitamin E alone or vitamin E and vitamin C in combination were given to AD patients [138], with the results being that CSF levels of vitamin E were increased. In the combination study, decreased susceptibility of lipoproteins to oxidation was found, consistent with the notions that vitamin C is able to regenerate the tocopheroxyl radical back to vitamin E, thus increasing antioxidant activity.

Moderately advanced AD patients were subjected to a clinical trial of high dose (2000 I.U.) vitamin E [142]. Delayed entry into nursing homes was found in the population of patients who received this high dose regimen. Although the progression of AD seemed to be slowed in these moderately advanced AD patients on high dose vitamin E, others have criticized this study as not directly showing efficacy of vitamin E [143]. However, based in part on the known oxidative stress in AD brain, the NIH is currently funding a multi-center clinical trial of high dose vitamin E in patients with the earliest sign of clincial memory loss, so-called mild cognitive impairment. The hypothesis is that early intervention with the antioxidant vitamin E will show more efficacy than with late-stage patients, and that vitamin E will significantly retard progression of this oxidative stress-related dementing disorder [144,145].

3.3. Polyphenols

Flavonoids from four different sources will be reviewed with respect to experimental data from *in vitro* and *in vivo* studies and clinical trials in AD.

3.3.1. Red wine

In the 1970s, studies [146] showing a correlation between a Mediterranean diet and low incidence of coronary and ischemic heart disease, raised public interest as to the effects of beverages such as red wine protecting against health problems and aging. Among the many phenolic compounds of wine, one that deserves to be mentioned is resveratrol. This polyphenol is produced by the grape in response to a mycelium infection and confers high resistance to its attack. Higher concentrations of resveratrol are found in red wines, especially in cabernet sauvignon grapes of Bordeaux.

The mechanism of antioxidant action of this natural compound has been extensively investigated [147], demonstrating that the para-hydroxyl group of trans-resveratrol is necessary for efficient scavenging activity. The beneficial effect has been tested in several studies. Frankel et al. [148] found that a 10 μM phenol-containing wine inhibited low density lipoprotein (LDL) oxidation more efficiently than vitamin E. In PC12 cells, resveratrol showed a protective effect against oxidative insult [149]. Others demonstrated that administration of resveratrol in rats protected the brain against excitotoxic damage [150] and in hippocampal neurons against nitric oxide-related toxicity [151].

The effects of red wine consumption in age-related dementia and AD were evaluated by several investigations. A French study [152] on a community of persons 65 years of age and older, whose only consumption of alcoholic beverages was represented by red wine in the amount considered

moderate (3 to 4 glasses per day), analyzed the incidence of dementia and AD compared to non-drinkers. After adjusting for age, sex, education and other factors, the study showed an inverse relationship between moderate wine drinking and AD incidence, suggesting that wine concumption may slow or prevent dementia. The same French investigators reported an epidemiological study on the effects of dietary wine flavonoids in preventing dementia in elderly. After a 5-year study on the dietary habits of 1,367 subjects, the authors concluded that the risk of developing dementia is lower for those subjects having a diet rich in flavonoids [153]. Taken together with the findings that resveratrol inhibits the oxidative and neurotoxic properties of Aβ [154], these results support a potentially beneficial effect of red wine in ameliorating the onset and symptoms of disorders associated with age, due to the powerful antioxidant effect of polyphenols.

3.3.2. Ginkgo biloba

Modern scientific studies on the biological activity of extracts from dried ginkgo biloba leaves started 20 years ago, even though the beneficial effects of these natural substances were known for 5000 years in traditional Chinese medicine. The ginkgo extracts that are currently used for medicinal purposes contain 24% flavonoids and 6% terpenoids. The antioxidant effects of flavonoids combined with the anti-inflammatory properties of the terpenoids bilobalide and ginkgolides A, B, C, M and J, terpenoids antagonists of platelet-activating factor (PAF), make these natural extracts plausible to use in Alzheimer's disease, characterized by both oxidative damage [3,155] and inflammation [156].

Extensive studies on Ginkgo extracts showed their ability to protect brain neurons from oxidative stress [157], to inhibit apoptosis [158] in cell culture, and to rescue PC12 neuronal cells from beta-amyloid-induced cell death [159].

In ROS-exposed mice [160], apoptosis was significantly reduced after pretreatment with Ginkgo extracts. In several cell lines, treatment with Ginkgo led to increased endogenous glutathione (GSH) and γ-glutamylcysteinyl synthase (γ-GCS) m-RNA [161].

Therapeutic use of Ginkgo biloba extracts in preventing and alleviating symptoms associated with cognitive disorders is largely employed in Europe. The standardized extract (EGb 761), recently approved in Germany for the treatment of dementia, has been widely used in clinical trials to assess the potentially beneficial effect in ameliorating pathological condition associated with dementia and AD. The abundance of investigations is mainly due to the demonstrated antioxidant properties of these natural extracts, in conjunction with their assessed safety, except for minor cases of diarrhea, vomiting and restlessness [162]. However, criteria such as sufficient statistical analysis, standardized tests for AD diagnosis, and use of standardized Gingko extracts in any stated dose were not met by the majority of these studies [162]. A placebo-controlled, double-blind randomized trial of Ginkgo was performed to establish the effects of a one year treatment on 202 AD patients [163]. The authors reported that the extract stabilized and improved cognitive performance of their AD patients.

In a recent study on the pharmacological effect of EGb in comparison with tacrine (Cognex^R), one of the anti-dementia drugs approved by the FDA, a pharmaco-electroencephalogram method was applied. The effect of tacrine in stimulating brain bioelectrical activity was also seen in EGb-treated subjects, but more cognitive activator EEG profiles were recorded after treatment with EGb than tacrine [164]. However, this significant result was not accompanied by any study on the therapeutic effects of these substances. The most recent trial [165], showed that a 52 weeks treatment with 120 mg of EGb in demented patients, resulted in a mild, but significant, improvement in cognitive assessment. All these reports taken together with studies that show protection against oxidative stress and neurotoxicity from Aβ by Ginkgo biloba [159], suggest a potential beneficial effect of Ginkgo to attenuate the effects of cognitive decline associated with AD, likely through amelioration of oxidative stress.

3.3.3. Green tea

Polyphenolic compounds are highly abundant in tea leaves, where they make up more than 30% of the dry weight of the leaf. The main flavonoids present in green tea are catechins, in particular epigallocatechin gallate (EGCG), in the amount of 30–130 mg per cup of tea. Other polyphenolic compounds such as quercetin, kaempfenol, myricetin and their glycosides are found in lower concentration. The different properties exhibited by these compounds have been tested by a variety of studies in cell lines. Tea catechins have been shown to possess anticarcinogenic [166], antiallergenic [167] and antiapoptotic properties. In hippocampal neurons, tea polyphenols show a protective effect against ischemic insult [168], while neurotoxicity induced by Aβ (1–42), whose deposition in the brain accompanies neuronal loss in AD, was attenuated in the presence of EGCG [169]. The protective antioxidant effect of these natural compounds was also confirmed by other studies in synaptosomes [170].

The importance of these compounds in humans has been extensively studied. The bioavailability of tea polyphenols, the concentration of which increases up to 1 μM in human plasma after tea consumption [171], renders these natural substances very interesting in potential prevention and treatment of those pathologies, such as AD, where oxidative stress plays an important role in neurodegeneration. Several human studies [172,173] report an increased radical scavenging and ferrous iron-reducing activity of plasma after consumption of tea polyphenols, demonstrating that green tea enhances natural antioxidant defenses. Due to the lack of evidence on the capability of tea flavonoids of crossing the blood brain barrier, the effects of these compounds in the progression of neurodegenerative disorders have not been tested in large scale. Two small case-control studies on AD

[174,175] did not report any significant result relative to tea consumption, while a large investigation on Parkinson's disease (PD) found a moderate risk reduction compared to non–tea-drinkers [176]. More accurate data on the relationship between green tea consumption and occurrence of AD have yet to be obtained, although the findings outlined above, taken together with the observation that EGCG inhibits Aβ-induced oxidative stress and neurotoxicity, suggest green tea extracts as potentially promising therapeutic agents for AD.

3.3.4. Blueberries

The flavonoids contained in these berries, mainly anthocyanins, have been extensively studied *in vitro* and *in vivo* to assess their action in several pathologies [177]. These compounds display vasoprotective [178], anticancer and anti-inflammatory properties. In aged rats, blueberry extracts were effective in reversing age-related decline with cognitive, motor and neuronal effects [179]. These results are consistent with an investigation on the effects of anthocyanins in defending against oxidative stress [48]. Polyphenolics were capable of enhancing red blood cell resistance to oxidative stress *in vitro* and *in vivo*, supporting the idea of a protective role of these substances in ROS-mediated, age-related neurological decline. Although there are no studies on the action of blueberry extracts in ameliorating AD cognitive decline, behavior and memory improvement has been reported in transgenic mice with APP/PS-1 double mutations, a model for AD [180]. Taken together, these studies suggest that blueberry polyphenols may show beneficial effects in protecting and reversing the course of neurological aging associated with AD. More studies remain to be performed.

3.3.5. Curcumin and caffeic phenyl ester

Neuroprotective effects of curcumin have been demonstrated by Rajakrishnan [181] in ethanol-induced brain damage, in which oral administration of curcumin to rats caused a significant reversal in lipid peroxidation, brain lipid modifications, as well as increase in glutathione levels. This finding is in agreement with other studies demonstrating that curcumin can increase the activity of γ-glutamyl-cysteinyl synthetase and other GSH-linked detoxifying enzymes [182]. As a result of the strong interest focused on the discovery of natural compounds endowed with Aβ-toxicity-modulating properties, curcumin was shown to protect PC12 and human endothelial cells from Aβ (1–42) oxidative insult [25].

Recent epidemiological studies [183] have raised the possibility that this molecule, as one of the most prevalent nutritional and medicinal compounds used by Asian Indian population, is responsible for the significantly reduced (4.4-fold) prevalence of AD in India compared to United States. Based on these findings, Lim and colleagues [23] have provided compelling evidence that dietary curcumin given to an Alzheimer transgenic APPSw mouse model (Tg2576) for 6 months resulted in a suppression of indices of inflammation and oxidative damage in the brain of these mice. Indeed, a significant decrease of oxidized protein and interleukin-1β, a proinflammatory cytokine usually elevated in the brain of these mice, was observed in association with a 43–50% reduction in insoluble Aβ, soluble Aβ and plaque burden. The astrocytic marker GFAP, generally associated with injury and inflammatory processes, as well as neuronal micorgliosis were significantly reduced by curcumin treatment. Interestingly, oxidized proteins were not reduced in ibuprofen-treated Tg2576 mice [23]. In view of the fact that ibuprofen reduces inflammation indexed by IL-1β and plaque-associated microgliosis, this finding strongly suggests that reactive oxygen species secondary to inflammation in plaque-associated reactive glia are not the primary causative factor leading to oxidative damage in this β-amyloidosis model. Consequently, a combination of antioxidants and non-steroidal anti-inflammatory drugs should be considered as an approach to AD prevention or therapeutics.

Similar findings have been demonstrated in rats after Aβ-induced brain damage in which curcumin, unlike conventional NSAIDs, reversed cognitive deficits and neuropathology as indicated by suppression of isoprostane levels (lipid peroxdidation product) and post-synaptic density (PSD)-95 loss, recovery of spatial memory deficits in the Morris Water Maze, and reduction of Aβ deposits [184]. Furthermore, Kuner and coworkers [185] using a human neuroblastoma cell line to investigate the involvement of p57NTR (a nonselective neurotrophin receptor, belonging to the death receptor family and thought as a receptor for Aβ-induced neurotoxicity) in NFκB activation and apoptotic cell death, have recently shown that curcumin was capable to inhibit NFκB activation, thus preventing neuronal cell death.

Potential mechanisms underlying these multiple effects have been considered to be multifactorial [23]. Curcumin suppressed microgliosis in neuronal layers but even increased microglia adjacent to plaques, raising the interesting possibility that this polyphenol may stimulate microglial phagocytosis of amyloid. In addition, curcumin inhibited proamyloidogenic pathways by regulating cholesterol levels. Recently, it has been demonstrated that cholesterol could promote amyloidogenicity by regulating β- and γ-secretase activity [186]. Curcumin also was found to be a strong anti-amyloidogenic factor by inhibiting both α-1-antichymotrypsin and NFκB-mediated transcription of $ApoE_4$ [187] as well as lipoxygenases and phospholipases D [188]. The capability of blocking multiple pathways potentially important in AD pathophysiology confers to the curcumin molecule a greater therapeutic potential for targeting, in addition to inflammation-related events that may be involved in neurodegeneration in AD.

Consistent with this notion is the recent finding that amyloid precursor protein as well as amyloid precursor-like protein, by binding to heme oxygenase, leads to inhibition of HO activity, and hence influences neurotoxic pathways

[189]. This finding highlights the important role of curcumin as a heat shock response inducer and cytoprotectant, and substantiates the notion that many of the biological actions of curcumin, including inhibition of cell proliferation [190], antioxidant potential [87] and modulation of inflammatory response [69], can be ascribed to overexpression of HO-1 [191–193]. Curcumin is a potent inducer of HO-1 in vascular endothelial cells, and tin protophorphyrin IX, an inhibitor of HO activity, abolished curcumin-mediated cytoprotection against oxidative stress [194].

In astroglial cells the role of caffeic acid phenethyl ester (CAPE), an active component of propolis, recently was demonstrated to be a novel HO-1 inducer [195]. This study also provides experimental evidence that both CAPE- and curcumin-mediated HO-1 induction was not affected by thiols, suggesting alternative mechanisms in the regulation of HO-1 expression by polyphenolic compounds. The similarity of CAPE to curcumin is striking because CAPE is also a Michael reaction acceptor that has a broad spectrum of biological activities, including anti-inflammatory, antioxidant and anticancer effects [196,197]. These agents all appear capable of transcriptionally activating a gene battery that includes NAD(P)H:quinone oxidoreductase, aldo-keto reductases, glutathione S-transferases, γ-glutamylcysteine synthetase, glutathione synthetase and heme oxygenase [198]. Gene induction occurs through the antioxidant responsive element (ARE), a process that is dependent on the Nuclear Factor-Erythroid 2p45-related factors, Nrf1 and Nrf2 [199,200]. Under basal conditions, these basic region leucine zipper (bZIP) transcription factors are located in the cytoplasm and, upon challenge with inducing agents, they translocate to the nucleus. Within the nucleus, Nrf1 and Nrf2 are recruited to the ARE as heterodimers with either small Maf proteins, FosB, c-Jun, JunD, activating transcription factor 2 (ATF2) or ATF4. The role of protein kinases in transducing chemical stress signals to the bZIP factors that affect gene induction through the ARE is emerging as an important mechanism for activation of cytoprotective antioxidant genes, such as HO or phase II detoxifying enzymes (GSH transferase and quinone oxido reductase). Thus, increased expression of genes regulated by the ARE/EpRE in cells of the central nervous system may provide protection against oxidative stress [201].

Increasing evidence indicates that mitogen-activated protein kinase pathways, which play an important role in mediating extracellular signals, such as mitogenic signaling (extracellular signal-regulated kinase, ERK) or cellular stress signaling (JNK/SAPK and P38) from membrane to the nucleus, is misregulated during the course of AD. Intriguingly, the "two hits" hypothesis of mitogenic and oxidative stress-induced, as recently proposed [202], suggests that both oxidative stress and abnormalities in mitotic signaling can independently serve to initiate, but both are necessary to propagate disease pathogenesis. Conceivably, dietary supplementation with polyphenolic agents, such as curcumin and its derivatives, can forestall the development of AD consistently with a major "metabolic" component to this disorder, and hence provides optimism for dietary therapies for AD.

4. Conclusion

With the increasingly aging population of the United States, the number of AD patients is predicted to reach 14 million in the mid-21st century in the absence of effective interventions [203]. This will pose an immense economic and personal burden on the people of this country. Similar considerations apply worldwide, except in sub-Sahara Africa, where HIV infection rates seem to be leading to decreased incidence of AD [203]. One therapeutic strategy is to delay the onset of AD dementia sufficiently long as to slow the neuronal damage associated with Aβ-induced oxidative stress, particularly Aβ-induced lipid peroxidation. Prevention of lipid peroxidation would lead to decreased levels of reactive alkenals like HNE and acrolein, which, in turn, would lead to decreased oxidative modification of important transport proteins, such as the glutatmate transporter. Consequently, less excitotoxic neuronal death would occur. Delay of the onset of AD would permit one's cognitive ability to remain intact, even if diminished somewhat, and would allow other age-related mechanisms of death to occur prior to dementia, e.g., cancer, heart disease, stroke, etc.

Brain-accessible antioxidants potentially may provide the means of implementing this therapeutic strategy of delaying the onset of AD. And one source of such antioxidants may be through the diet. In this review, studies with AD patients and animal AD models using various brain accessible antioxidants including thiol-containing antioxidants, vitamins and polyphenols are outlined. Although not all compounds are effective, the consensus of studies suggests that nutritionally derived sources of brain accessible antioxidants may provide an approach to slow the onset and progression of the devastating dementing disorder. Continued studies to test this notion in AD and animal models of this disease is, in our opinion, warranted by the success of prior investigations.

Note in proof

Recent studies have suggested that a diet rich in vitamins E and C significantly lower the risk of developing Alzheimer's disease [211,212], consistent with the notion that oxidative stress underlies the molecular pathogenesis of this dementing disorder [2–5].

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