JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

J. Agric. Food Chem. **2008,** *56,* 4855–4873 **4855**

REVIEWS

Challenges for Research on Polyphenols from Foods in Alzheimer's Disease: Bioavailability, Metabolism, and Cellular and Molecular Mechanisms

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Polyphenols are the most abundant antioxidants in diet. Indeed, fruits, vegetables, beverages (tea, wine, juices), plants, and some herbs are loaded with powerful antioxidant polyphenols. Despite their wide distribution, research on human health benefits truly began in the mid-1990s (Scalbert, A.; Johnson, I. T.; Saltmarsh, M. *Am. J. Clin. Nutr.* **2005**, *81*, S15S−217S). Phenolic compounds have been receiving increasing interest from consumers and manufacturers because numerous epidemiological studies have suggested associations between consumption of polyphenol-rich foods or beverages and the prevention of certain chronic diseases such as cancers and cardiovascular diseases (Manach, C.; Mazur, A.; Scalbert, A. *Curr. Opin. Lipidol.* **2005**, *16*, 77-84; Duthie, S. *J. Mol. Nutr. Food Res.* **2007**, *51*, 665−674). Furthermore, in the past 10 years, research on the neuroprotective effects of dietary polyphenols has developed considerably. These compounds are able to protect neuronal cells in various in vivo and in vitro models through different intracellular targets (Ramassamy, C. *Eur. J. Pharmacol.* **2006**, *545*, 51−64). However, it is not at all clear whether these compounds reach the brain in sufficient concentrations and in a biologically active form to exert beneficial effects. On the other hand, it has become clear that the mechanisms of action of these polyphenols go beyond their antioxidant activity and the attenuation of oxidative stress. Therefore, there is a need for more research on their intracellular and molecular targets as special pathways underlying distinct polyphenol-induced neuroprotection. The focus of this review is aimed at presenting the role of some polyphenols from fruits, vegetables, and beverages in neuroprotection and particularly in Alzheimer's disease and the research challenges in this area.

KEYWORDS: Antioxidant; neuroprotection; catechins; resveratrol; curcumin; berries; pomegranate; NRf2; MAPKs

I. OXIDATIVE STRESS IN AGING AND ALZHEIMER'S DISEASE (AD)

I.1. Oxidatively Induced Damage in Aging Brain. Free radicals can de defined as molecules or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals. These unpaired electrons give a considerable degree of reactivity to free radicals. Reactive oxygen species (ROS), as well as reactive nitrogen species (RNS), are products of normal cellular metabolism. Both reactive species are now well-recognized as playing a dual role in both deleterious and beneficial effects, especially in numerous signal transduction mechanisms. Radicals derived from oxygen represent the most important class of radical species generated in living systems. For instance, superoxide anion ($O_2^{\bullet -}$) is considered to be the *primary* ROS and can further interact with other molecules to generate *secondary* ROS, either through enzyme- or metal-catalyzed processes. These anions are mostly produced in the mitochondria by complexes I and III of the electron transport chain. The hydroxyl radical ($OH^{\bullet}$) has a high reactivity, making it a very toxic radical with a very short half-life. Hydroxyl radicals are mostly produced through the Fenton reaction, which requires Fe^{2+}. Additional ROS that can be formed in living

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10.1021/jf0735073 CCC: $40.75
Published on Web 06/17/2008

systems are peroxyl radicals ($ROO^{\bullet}$), particularly through the reaction of hydroxyl radicals with unsaturated lipids.

Nitric oxide ($NO^{\bullet}$) is a small molecule that contains a single unpaired electron and is therefore a free radical. $NO^{\bullet}$ is generated in biological tissues by nitric oxide synthases (NOSs), which metabolize arginine to citrulline with the formation of $NO^{\bullet}$. $NO^{\bullet}$ is an abundant reactive radical that acts as an important oxidative biological signaling molecule in diverse physiological phenomena, including neurotransmission, smooth muscle relaxation, immune regulation, and blood pressure regulation, etc. An overproduction of RNS causes nitrosative stress. This may occur when the generation of reactive nitrogen species exceeds the system's ability to neutralize and eliminate them. Nitrosative stress may lead to unwanted nitrosylation reactions that alter the structure and functions of certain proteins.

At high concentrations, ROS and RNS can be important mediators of damage to nucleic acids, lipids, and proteins. In the brain, these damages contribute to aging and age-associated neurodegenerative diseases such as Alzheimer's disease (AD) or Parkinson's disease.

Brain aging is associated with the accumulation of these oxidative-induced damages, likely due to the imbalance between antioxidant defenses and intracellular generation of ROS. The overall rationale implication of oxidative stress in aging brain is based on the following premises: (a) the brain contains high levels of unsaturated fatty acids, which are vulnerable to oxidation (it is particularly high in 20:4 and 22:6 fatty acids); (b) the brain consumes high amounts of oxygen (about 20% of the total amount used in the body); (c) levels of antioxidants are lower in the brain; and (d) the brain contains high concentrations of transition metals such as Fe^{2+} that are key catalysts of oxidative-induced damages.

In the brain, oxidative damage to DNA occurs continuously, resulting in damaged nucleotides and strand breaks. It has been estimated that 10000 oxidative interactions occur between DNA and endogenously generated free radicals per human cell per day. One of the most widely studied base lesions is 8-hydroxy-2′-deoxyguanosine (8-OHdG), a hydroxyl radical-damaged guanine nucleoside. Several studies have demonstrated that the level of 8-OHdG is elevated in old brains, with a 4-fold increase when compared to young brains (*5*). In mitochondria, higher levels of oxidative damage and DNA mutations have been ascribed to the location of the DNA near the inner mitochondrial membrane sites where superoxide anions are mainly formed.

Accumulation of oxidized proteins in brain is widely considered a hallmark of aging (*6–8*) with increases of nearly 2- and 4-fold in humans and rats, respectively (*6*). Oxidatively induced damage to proteins can affect virtually all amino acids, with sulfur-containing amino acids and aromatic amino acids being the most susceptible (*9*). The amount of oxidized protein is influenced not only by its rate of formation, but also by its rate of degradation. In a functioning system oxidized proteins are degraded by the proteasomal/protease system, which is responsible for removing damaged proteins that form insoluble aggregates (*10*). During aging, proteasome activity also declines (*10*), and this could contribute to the elevation of oxidized proteins. Lipid peroxidation yields a large number of compounds such as malondialdehyde (MDA), 4-hydroxynonenal (HNE), F_2-isoprostanes, and acrolein. The most widely studied are the active aldehydes and isoprostanes. A set of isoprostanes that could be uniquely formed in brain from peroxidation of docosahexanoic acid are neuroprostanes (*11*). HNE is the major product formed from peroxidation of ω-6-conjugated fatty acids, such as arachidonic acid and linoleic acid (*12*). HNE is biologically active, causing gene induction (antioxidant genes) and cytotoxicity; it can react with many biological molecules including various amino acids, proteins, and bases in DNA.

Lipid peroxidation has been reported to be elevated in the brain with age. MDA was increased in the cytoplasm of neurons and astrocytes in normal aging, but was rarely detected in normal young subjects. In the hippocampus, neuronal and glial MDA deposition was marked in the CA4 region but mild in CA1 (*13*). Morevover, the lipid peroxidation products, MDA, HNE, and acrolein, have been reported to react with DNA and proteins to produce further damage in aged brains (*14*). Age-related modifications of multiple biomolecules by oxidative damages may affect brain health and function in the long run. These changes observed in normal aging are exacerbated in various neurodegenerative diseases related to aging.

I.2. Oxidative Damage to Lipids, Proteins, and Nucleic Acids in Mild Cognitive Impairment and in AD. Aging may be regarded as the major risk factor for all forms of dementia and particularly for AD, affecting up to 18 million people worldwide (*15*). According to the Alzheimer's Society, this number could reach 34 million by 2025 (*15*). Its prevalence doubles approximately every five years after the age of 60, with 1 in 10 individuals over 65 years and nearly half of those over 85 being affected by the disease. AD causes one of the greatest threats to the future of the healthcare system, with the anticipated demographic shift to an aging population.

AD is multifactorial, with a complex combination of genetic and nongenetic components. The early-onset familial form represents only a small fraction of all AD cases ($\leq$5%) and typically presents itself with age of onset younger than 65 years, whereas the nongenetic or sporadic form represents the majority of AD cases. To date, mutations on three genes have been reported to cause the early-onset familial form of AD. These include the genes coding for the amyloid precursor protein (APP) on chromosome 21, presenilin 1 on chromosome 14, and presenilin 2 on chromosome 1 (*16–18*). Although these AD-causing mutations occur in three different genes located on three different chromosomes, they all share a common biochemical pathway, that is, the altered production of the amyloid β peptide (Aβ), which leads to neuronal death and dementia.

Aβ is released after the cleavage of APP by β- and γ-secretases, respectively. β-Secretase has been identified as an aspartic protease, and γ-secretase can cleave APP at the C-terminal end of Aβ at different sites, giving rise to Aβ peptides that are 39−43 amino acids long. The exact location of C-terminal cleavage is critical, because generation of the more amyloidogenic peptides (such as $A\beta_{1-42}$) is strongly correlated with AD development.

On the other hand, the late-onset form of AD, representing the vast majority of all AD cases, has one common genetic risk factor, the ϵ4 allele of the apolipoprotein E gene (APOE) located on chromosome 19q13 (*19–21*). The increased risk with the ϵ4 allele of the apolipoprotein E has been consistently replicated in a large number of studies across many ethnic groups. Unlike the mutations in the known early-onset familial form genes, the ϵ4 allele of the apolipoprotein E is neither necessary nor sufficient to cause AD but instead operates as a genetic risk factor by decreasing the age of onset in a dose-dependent manner.

ApoE is a plasma glycoprotein with a molecular mass of 34 kDa, synthesized mainly by the liver, neurons and astrocytes in the brain, and other cell types including macrophages and monocytes. A polymorphism of APOE in human serum has been described by isoelectric focusing, which determined the three major isoforms of ApoE (ApoE2, ApoE3, and ApoE4). A single

locus with three alleles (E2, E3, and E4) is responsible for this pattern. The ApoE2, ApoE3, and ApoE4 isoforms differ in amino acid sequence at two sites (residues 112 and 158), with apoE2 containing cysteine residues and apoE4 containing arginine residues at both sites, whereas apoE3 contains cysteine and arginine at positions 112 and 158, respectively. ApoE is a major apolipoprotein in the brain involved in the redistribution of lipids through the low-density lipoprotein and related receptors (*5*). Apolipoprotein E4 has been reported to increase Aβ production as well as inhibit clearance (*22, 23*).

Although a large number of genes have been shown to be associated with AD (*24*), the exact nature of their relation to AD development is still unclear. In addition to these genetic components, there is considerable evidence that oxidative stress is an early and critical event in the pathogenesis of AD (*25–28*). For instance, isoprostanes, derived from free radical oxidation of docosahexaenoic acid, are increased in brain cortex (*28–30*). Interestingly, F-$_2$-isoprostanes, prostaglandin-like compounds derived from free radical-catalyzed peroxidation of arachidonic acid, are also elevated in the plasma, urine, and cerebrospinal fluid of patients with AD (*32*). Moreover, we and others have demonstrated that the level of lipid peroxidation in the AD brain is dependent on the apoE genotype and level (*30–33*). Increased levels of HNE and acrolein in different brain areas were also described in the hippocampus/parahippocampal gyrus and cerebellum in subjects with mild cognitive impairment as compared to control subjects (*35*). Both byproducts of lipid peroxidation are known to be neurotoxic and can affect neuronal functions (*36, 37*).

Protein carbonyls and 3-nitrotyrosine, which are the markers of protein oxidation, are also elevated in AD (*38, 39*). Protein carbonyls are present in both tangle- and non-tangle-bearing neurons (*40*), in the frontal lobe or hippocampus (*41, 42*). Nitrotyrosine and dityrosine cross-linked proteins are elevated 8- and 3-fold, respectively, in the hippocampus and neocortical regions of AD brain as compared to age-matched controls (*43*). By using redox proteomics, specific elevation of oxidatively modified proteins has been identified in the hippocampus and the parietal lobe of the AD brain, such as α-enolase, heat shock cognate 71 (HSC 71), creatine kinase BB (CK BB), glutamine synthase (GS), and ubiquitin carboxy-terminal hydrolase L-1 (UCHL-1) (*44, 45*).

It has been found that levels of multiple oxidized bases from nuclear and mitochondrial DNA in the AD brain were significantly higher in the frontal, parietal, and temporal lobes as compared to control brain regions (*46*). Moreover, mitochondrial DNA had approximately 10-fold higher levels of oxidized bases than nuclear DNA. These data are consistent with higher levels of oxidative stress in mitochondria. 8-OHdG, a widely studied biomarker of DNA damage, was approximately 10-fold higher than other oxidized base adducts in both AD and control subjects. DNA from the temporal lobe showed the most oxidative damage, whereas the cerebellum was only slightly affected in AD brains. These results suggest that oxidative damage to mitochondrial DNA may contribute to the neurodegeneration observed in AD. DNA repair mechanisms have a critical role in protecting the genome. Several studies have shown a decline in the repair of 8-OHdG in AD (*47, 48*). RNA oxidation is also an important event in the pathogenesis of AD as up to 50% of mRNAs purified from AD frontal cortices were oxidized (*49*) and RNA oxidation occurred to a large extent in those neurons that are especially vulnerable to degeneration in AD (*50*).

Further evidence of oxidative stress in AD is the modification of antioxidant activity in the brain. For instance, we have demonstrated that catalase activity is higher and glutathione level is lower in AD (*30*). The glutathione transferase activity, which is responsible for HNE clearance, is decreased in several regions of the AD brain including the hippocampus (*51*).

There is now substantial evidence indicating that oxidative damage to the brain is an early event in the pathogenesis of AD as lipid and protein as well as DNA and RNA oxidations are elevated in mild cognitive impairment (MCI) (*52, 53*), a condition that is a transistion phase between control and AD (*54, 55*). MCI patients suffer from a decline in cognition without signs of dementia, with activities of daily living relatively unaffected. Pathologically, MCI has also been characterized by using magnetic resonance imaging technology, to show measurable atrophy in the hippocampus and entorhinal cortex (*56, 57*), both neurodegenerated areas in AD. These studies establish oxidative damage as an early event in the pathogenesis of AD that can serve as a therapeutic target to slow the progression or perhaps the onset of the disease (*54*).

The Aβ peptide, which is responsible for senile plaque formation in AD brain, has been reported to generate hydrogen peroxide from molecular oxygen through electron transfer interactions involving bound redox-active metal ions (*58–61*). Aβ has high affinity for both copper and zinc (*62*), and both Aβ and APP display strong copper reductase activity, generating Cu^+ from Cu^{2+}.

The original amyloid cascade hypothesis claimed that the fibrilized form of A$\beta\beta$ (fAβ) was the main component of senile plaques (*63*). Because many processes of AD were not explained by fAβ, there is still no clear consensus on the precise nature of the toxic form of Aβ, but recent attention has focused on early protein assemblies [protofibrils, soluble oligomers, Aβ-derived diffusible ligands (ADDLs), or globular neurotoxins]. Therefore, the effects of Aβ could depend on its aggregation state (*64*). On the basis of these findings, it has been proposed that Aβ acts through a biphasic neurotoxic mechanism that is conformation dependent.

Besides its ability to induce oxidative stress, Aβ could also lead to activation of some redox-sensitive transcription factors such as NF-κB, extracellular protein regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 of mitogen-activated protein kinases (MAPKs) pathways. We and others have demonstrated that activation of these stress MAPKs may eventually lead to cell death (*65, 66*). These pathways are potential targets of polyphenolic compounds from fruits and vegetables. Altogether, these studies and others demonstrate that oxidative stress is involved in the pathophysiology of AD; therefore, intake of antioxidants may be beneficial in the prevention of AD.

II. CLASSIFICATION, BIOAVAILABILITY, AND METABOLISM OF POLYPHENOLS

II.1. Classification of Polyphenols. One of the major difficulties of elucidating the beneficial effects of polyphenols is the large number of polyphenolic compounds found in fruits, vegetables, and beverages and the even larger numbers of their metabolites (**Figure 1**). Moreover, their bioavailability differs from one consumer to another in addition to intraindividual response occurring with physiopathological conditions.

For a number of reasons it is extremely difficult to estimate the daily average intake of polyphenols. One is the considerable diversity of the chemical structures of polyphenols, making the estimation of their content in food complex. Moreover, polyphenol intake depends on analytical methods, variation of content

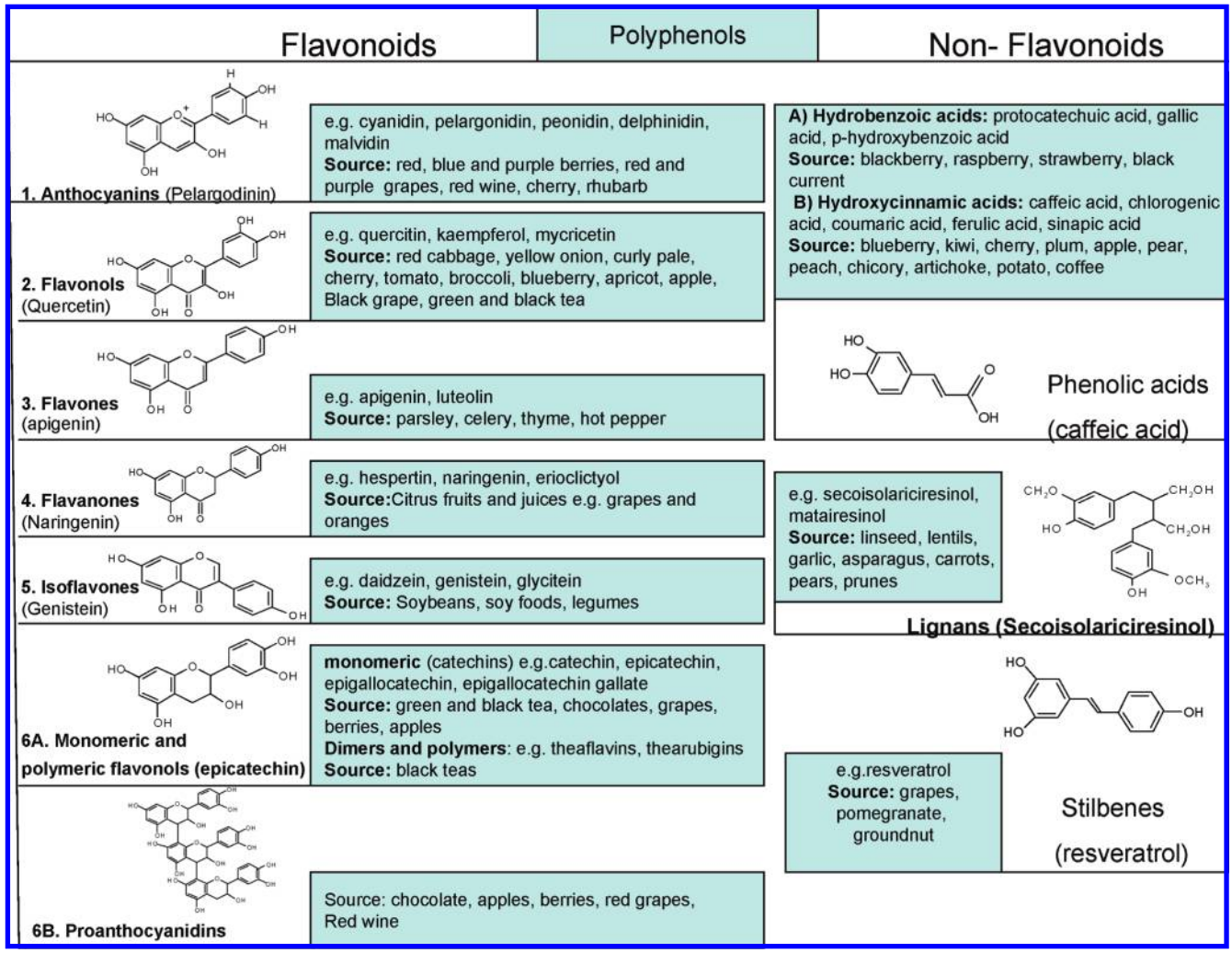


Figure 1. Main groups of polyphenols with their individual compounds and food sources.

in particular foods, geographical distribution, and seasonal variations, as well as habits of people, that is, tea, coffee, and wine consumption. For instance, Halvorsen et al. have screened the total antioxidant capacity of a variety of dietary fruits and vegetables by the ferric reducing antioxidant power assay (FRAP) (*68*) and found that the content of polyphenols in fruits and vegetables varies with geographical region and cultivar (**Table 1**). Wu et al. have quantified the levels of anthocyanins in 100 common foods in the U.S. market and found that the concentrations of anthocyanins varied significantly among them, from 0.6 to 390 mg/100 g (*69*). On the basis of the intake data from NHANES 2001−2002 (National Health and Nutrition Examination Survey), they estimated that the consumption of total anthocyanins in the United States was around 12.5 mg/day (see **Table 2**) (*69*). This is 10 times higher than the intake of vitamin C and 100 times higher than the intake of vitamin E. The main dietary sources are fruits, vegetables and plant-derived beverages such as tea and red wine. The average intake of all flavonoids was found to be around 13 mg/day. Polyphenols can be broadly divided into two categories, flavonoids and nonflavonoid polyphenols. Nonflavonoids and phenolic acids are abundant in foods. Flavonoids, the target class of polyphenols, may be divided into different subclasses according to the degree of oxidation of the heterocyclic ring: anthocyanins, flavonols, flavans, flavanol, flavones, and isoflavones. In general, they are hydroxylated, methoxylated, and/or glycosylated derivatives (except catechins) (*71, 72*). The linked sugar is often glucose or rhamnose. The number of sugar moieties is commonly one, but could be two or three, and there are several positions of substitution on the polyphenol.

Quercetin, present in many fruits, vegetables, and beverages, is the main flavonol in our diet, and its mean intake was estimated around 16 mg/day (*73*). Anthocyanins are pigments of red fruits such as berries, grapes, and strawberries, and their contents could vary from 0.15 to 4.5 mg/g in fresh fruit. The main flavanols are catechins. These compounds are abundant in tea, and an infusion of green tea could contain 1 g/L catechins, whereas in black tea, their content is reduced to about half of this value due to their oxidation into more complex polyphenols during fermentation (*74*). Other sources of catechins are red wines (*34*) and chocolate (*67*) (**Table 3**). Flavones are less common and were identified in sweet red pepper (luteolin) and celery (apigenin) (*73*). Flavanones are mainly found in citrus fruits, hesperidin from oranges being the most widely consumed. The main source of isoflavones is soy, which contains around 1 mg of genistein and daidzein/g of dry bean (*75*). Both isoflavones have received considerable attention due to their estrogenic properties (*76*). Proanthocyanidins are polymeric flavanols and are usually present in plants. They are responsible for the astringency of food, and common sources are apples, pears, grapes, red wine, tea, and chocolate. Stilbenes are not widely found in food plants. Nevertheless, the stilbene resveratrol found in red wine has recently received great attention for its anticarcinogenic properties and for its neuroprotective effect.

Table 1. Total Antioxidant Concentrations of Fruits Determined by the FRAP Assay[a]

	sample A	mmol/ 100 g	sample B	mmol/ 100 g	sample C	mmol/ 100 g	overall mean
			Fruits				
grape	Carmel, Israel ($n = 3$)	2.42	Chiquita, Chile ($n = 3$)	1.02	Del Monte, Chile ($n = 3$)	0.9	1.45
orange	Spain	1.5	Outspan, Holland ($n = 3$)	1.08	Zenta ($n = 3$)	0.83	1.14
plum	Red Beauty, Ciruella, Spain ($n = 3$)	1.42	Herman, Norway ($n = 3$)	1.02	Forlimpopoli, Italy ($n = 3$)	0.73	1.06
pineapple	Del Monte, Costa Rica ($n = 3$)	1.36	Ivory Coast ($n = 3$)	0.39	Del Monte, Costa Rica ($n = 3$)	1.36	1.04
lemon	Dana, Spain ($n = 3$)	1.03	Dana, Spain ($n = 3$)	1.05	Dana, Spain ($n = 3$)	0.99	1.02
kiwi fruit	yellow, Zespri, New Zealand ($n = 3$)	1.29	green, Zespri, New Zealand	1.02	France ($n = 3$)	0.43	0.91
grapefruit	red, Dole, Honduras ($n = 3$)	0.81	yellow, Jaffa, Israel ($n = 3$)	0.82	red, Dole, Honduras ($n = 3$)	0.87	0.83
fig	Smyrna, Turkey ($n = 3$)	0.81	Smyrna, Turkey ($n = 3$)	0.75	Smyrna, Turkey ($n = 3$)	0.64	0.73
papaya	Mali ($n = 1$)	0.34	Dana, Brazil ($n = 3$)	0.75	Dana, Brazil ($n = 3$)	0.76	0.62
apricot	USA ($n = 3$)	0.52	USA ($n = 3$)	0.51	USA ($n = 3$)	0.52	0.52
mango	red, OJ, Pakistan ($n = 3$)	0.37	red, Dole, Brazil ($n = 3$)	0.33	yellow, La Bamba, Mexico ($n = 3$)	0.36	0.35
apple	Golden Delicious, New Zealand ($n = 3$)	0.15	Granny Smith, New Zealand	0.51	Gala, Italy ($n = 3$)	0.22	0.29
pear	Holland ($n = 3$)	0.2	Holland ($n = 3$)	0.19	Norway ($n = 3$)	0.16	0.18
horned melon	Kiviano, New Zealand ($n = 3$)	0.05	Pattern, Mali ($n = 1$)	0.15	yellow, Mali ($n = 1$)	0.29	0.16
			Vegetables				
Brussels sprout	Spain ($n = 3$)	1.31	Content, Norway ($n = 3$)	0.74	Spain ($n = 3$)	1.37	1.14
spinach	Vikong 290, Norway ($n = 3$)	1.1	Italy ($n = 3$)	0.96	Italy ($n = 3$)	0.87	0.98
asparagus	Agro Paracas, Peru ($n = 3$)	0.79	Agro Paracas, Peru ($n = 3$)	0.8	Agro Paracas, Peru ($n = 3$)	0.97	0.85
celery	Mali ($n = 3$)	0.8					0.8
artichoke heart	Italy ($n = 3$)	0.71	Italy ($n = 3$)	0.67	Italy ($n = 3$)	0.69	0.69
onion	red, Italy ($n = 3$)	0.7	yellow, Italy ($n = 3$)	0.63	Red Baron, Norway ($n = 3$)	0.67	0.67
broccoli	Norway ($n = 3$)	0.35	Spain ($n = 3$)	0.63	Spain ($n = 3$)	0.77	0.58
avocado	Spain ($n = 3$)	0.6	Israel ($n = 3$)	0.18	Spain ($n = 3$)	0.44	0.41
Savoy cabbage	Taler, Norway ($n = 3$)	0.4	Norway ($n = 3$)	0.41	Norway ($n = 3$)	0.43	0.41
radish	France ($n = 3$)	0.39	France ($n = 3$)	0.42	Holland ($n = 3$)	0.39	0.4
tomato	cherry tomato, Holland ($n = 3$)	0.34	plum tomato, Spain ($n = 3$)	0.24	Mali ($n = 2$)	0.34	0.31
garlic, dried	Holland ($n = 3$)	0.24	USA ($n = 3$)	0.23	USA ($n = 3$)	0.24	0.24
cauliflower	Freemont, Norway ($n = 3$)	0.13	Alverda, Norway ($n = 3$)	0.22	Spain ($n = 3$)	0.35	0.23
garlic	Holland ($n = 3$)	0.19	Senegal ($n = 3$)	0.25	Mali ($n = 3$)	0.18	0.21
maize	Carmel, Israel ($n = 3$)	0.21	Spain ($n = 3$)	0.26	Mali ($n = 1$)	0.1	0.19
			Dried Fruits				
apricot	Diva, Turkey ($n = 3$)	3.27	Sunsweet, California ($n = 3$)	3.23	Diva, Turkey ($n = 3$)	3.23	3.24
prune	Diva, California ($n = 3$)	1.95	Sunsweet, California ($n = 3$)	2.17	Sunsweet, California ($n = 3$)	3.69	2.6
raisin	SunMaid, USA ($n = 3$)	0.92	Asteche, Spain ($n = 3$)	0.92	Korints, USA ($n = 3$)	0.57	0.8
fig	Smyrna, Italy ($n = 3$)	0.71	Smyrna, Italy ($n = 3$)	0.78	Smyrna, Italy ($n = 3$)	0.79	0.76

[a] Samples A−C represent separate samples of the same dietary plant obtained from different sources such as goegraphical location or manufacturers. The number of items analyzed is indicated in parentheses. Modified from Halvorsen et al. (*68*).

Lignans are mainly present in flaxseed and flaxseed oil. Their presence has been identified in plasma and in urine, and they could be metabolized by the gut microflora. Lignans are recognized as phytoestrogens due to their estrogen-like effect. Other unknown dietary polyphenols could also be generated after food fermentation, storage, or cooking. Usually, phenolic acids and non-flavonoid compounds account for about one-third of the total phenols, whereas flavonoids account for two-thirds.

II.2. Bioavailability and Metabolism. Bioavailability of polyphenols varies widely from one compound to another. It depends on their chemical structure, which determines their absorption rate through the gastroinstestinal tract, metabolism, and, therefore, biological activities. Most polyphenolics are poorly absorbed from the intestine and are highly metabolized, or rapidly eliminated. For instance, the maximal plasma concentrations of flavonoids are low, usually not more than 1 μmol/L, with a maximum level attained 1−2 h after ingestion. Therefore, the maintenance of a high concentration in plasma requires repeated ingestion of the polyphenols over time. Furthermore, the biological activities of the metabolites may differ from the parent compounds. Therefore, extensive research regarding their bioavailability and metabolism is required if their health effects are to be understood.

To determine whether certain polyphenols do in fact provide neuroprotection upon dietary exposure, it is important to understand how these compounds are absorbed by the body and where they are possibly further metabolized to biologically active or inactive metabolites. Polyphenols present as aglycones can be absorbed from the small intestine. However, most of them are present in the form of esters, glycosides, or polymers and are not easily absorbed in their natural form (*72*). Glycosylation influences chemical, physical, and biological properties of the flavonoids and their absorption. It is generally accepted that the breakdown of these conjugates to aglycones by acid hydrolysis in the stomach and by microflora in the gut is required to produce the bioactive components that are readily bioavailable to the body. However, relatively little is known about the ability of these aglycone polyphenolics to reach the target cells or what the influence of further metabolism in the body has on their spectra of biological activities. There are numerous sites important for the metabolism of dietary polyphenols, including the gastrointestinal tract, the liver, and various other tissues such as the skin and brain.

After hydrolysis of polyphenolic glucosides in the gastrointestinal tract, the aglycones are absorbed by the intestinal enterocytes. Here they undergo extensive glucuronide conjugation by UDP-glucuronyl transferase (UDP-GT) during their transfer from the gut to the portal vein (*77–81*). These conjugates of polyphenolics are the predominant form, present in the liver and other organs of the body. Polyphenolics containing a catechol (catechins, quercetin) moiety also undergo methylation by catechol-*O*-methyltransferase (COMT) (*82*). Other routes of metabolism in the gut are related to the antioxidant activities of the polyphenolics. Particularly, catechol-containing com-

Table 2. Estimation of Daily Consumption of Anthocyanins from Fruits, Vegetables, and Beverages [Modified from Wu et al. (*69*)]

food	anthocyanin (mg/100 g)	daily consumption (mg)
	Fruits (Raw)	
apple	0.6	0.7
blackberry	245	0.03
blueberry	365	3.39
cherry, sweet	122	0.56
cranberry	140	0.17
grape	36.7	1.77
nectarine	6.8	0.02
peach	4.8	0.12
plum	71.8	0.64
raspberry	390	0.93
strawberry	21.1	0.41
subtotal		8.75
	Vegetables (Raw)	
eggplant	85.7	0.13
cabbage, red	322	0.82
lettuce, red leaf	2.2	0.01
red radish	100	0.14
onion	12.1	0.96
bean, black	44.5	0.13
subtotal		2.19
	Nuts	
pistachio	7.5	0.004
subtotal		0.004
	Beverages	
grape juice	14.0	0.93
wine	10.7	0.66
subtotal		1.68
total		12.53

Table 3. Catechin Content in Various Food Sources [Modified from Sutherland et al. (*108*)]

food	catechin content
apples (16 varieties)	1000−7000 mg/kg of fresh cortex, mainly EC
apples (Jonagold)	17 mg/kg C + 129 mg/kg EC
beer	0.1−5.0 mg/L
black, red, and white currants	up to 30 mg/kg
blueberries	up to 30 mg/kg
cacao liquor	63 mg/L C + 577 mg/L EC
chocolate (baking-SRM) (b)	245 mg/kg C + 1220 mg/kg EC
chocolate (black)	610 mg/kg C + EC
chocolate (dark)	535 mg/kg
chocolate (milk)	159 mg/kg C + EC
cocoa	78 mg/L C + 132 mg/L EC
gooseberries	up to 30 mg/kg
grape seeds (*Vitis vinifera*)	1892 mg/kg C + 988 mg/kg EC + 353 mg/kg ECG
kiwi fruit	4.5 mg/kg of C + EC
strawberry	10−70 mg/kg C + 1 mg/kg EC
tea (black)	20 mg/L C + 37 mg/L EC + 73 mg/L ECG + 42 mg/L EGC + 128 mg/L EGCG
tea (green)	21 mg/L C + 98 mg/L EC + 90 mg/L ECG + 411 mg/L EGC + 444 mg/L EGCG
wine (red)	27−96 mg/L
wine grape (red)	800−4000 mg/kg

pounds such as catechins and quercetin may undergo oxidation in their role as antioxidants to form quinone-like structures that are detoxified by glutathione conjugation or broken down to smaller phenolic compounds (*78*), as has been observed in human skin fibroblasts (*81*). Once polyphenolics reach the liver, any remaining aglycone will undergo glucuronidation or sulfation and methylated polyphenolics may undergo demethylation.

The absorption of polyphenols also depends on the molecular weight. Because of their large molecular weight and their hydrosolubility, proanthocyanidins are poorly absorbed in the small intestine and are rapidly metabolized and eliminated (*83*).

Thus, the bioavailability and pharmacokinetics of polyphenolics are governed by a plethora of factors, that is, their native form (glycosylated/aglycone), the type of sugar moiety present, and their physiochemical properties. Moreover, some of the metabolites still possess inherent biological activities.

For instance, quercetin is readily taken up by Caco-2 human colon cancer cells, whereas its dietary forms 4′-monoglucoside and 3,4′-diglucoside are not. Studies have shown that of ingested quercetin <2% showed up in plasma. However, it is possible that quercetin remains in the epithelial cells of the gut, exerting its antioxidant effects locally to protect against colon cancer (*84–87*). Quercetin would then be metabolized in situ without reaching the plasma in significant concentrations. A study following the absorption and metabolism of radiolabeled quercetin-4′-glucoside in rats (7.6 mg/kg) found that >85% remained in the gut (either in its contents or its tissue) and about 6% was absorbed into the rest of the body, with about 3% found in plasma and 2% in liver (*88*). Most of the absorbed quercetin was in the form of diglucuronides, but more than 20 different glucuronidated, methylated, and/or sulfated metabolites were identified. Virtually no quercetin or its metabolites were detected in brain. This study demonstrates the great importance of the gastrointestinal tract and the relatively lesser important role of the liver in the metabolism of polyphenolic compounds, such as quercetin (*79, 88*). It also indicates that systemic bioavailability of quercetin is low and that bioavailability to the brain is almost negligible. It should be pointed out, however, that this is a rat study and that the uptake and metabolism of quercetin-4′-glucoside was followed for only 5 h. It could be suggested that greater concentrations of some quercetin metabolites may be found in certain tissues at later time points, although the results of Graf et al. (*88*) indicate that most metabolite concentrations in liver, for example, were decreasing after the first hour.

II.3. Uptake and Metabolism in the Brain. Oxidative stress and damage to brain macromolecules is an important process in neurodegenerative diseases. The antioxidant properties of many polyphenols is purported to provide neuroprotection. It is, however, not at all clear whether most of these compounds reach the brain in sufficient concentrations and in a biologically active form to have any beneficial effects. It is generally assumed that glucuronides have difficulty entering the cell and that conversion back to the unconjugated form by glucuronidases is required for cellular bioavailability. Clearly, it is the balance between these two forms at the target site that determines the biological effectiveness of these polyphenolic compounds.

Although numerous studies have reported flavonoid-mediated neuroprotection, there is little information about the interaction of flavonoids or their metabolites with the blood−brain barrier (BBB). The BBB is formed by the endothelium of brain microvessels, under the inductive influence of associated cells, especially astrocytes (*89*). Other transporters involved in the regulation of substrates across the blood−brain interface include the multidrug resistance-associated proteins (MRPs). The flavonoid epigallocatechin gallate, a polar polyphenol, has been reported to enter the brain after a gastric administration of [^{3}H]epigallocatechin gallate (*90*). The citrus flavonoids naringenin and hesperitin readily cross the BBB, whereas the less lipophilic glucuronide or glycoside conjugates have greater difficulty (*91*). It also appears that methylated flavonoids cross the BBB more readily than their phenolic counterparts (*92*).

III. ANTIOXIDANT ACTIVITIES OF POLYPHENOLS FROM FOODS

Flavonoids are the most widely studied class of polyphenols with respect to their antioxidant and biological activities. They have powerful antioxidant activities in vitro, being able to scavenge a wide range of ROS and RNS and chlorine species, such as superoxide, hydroxyl and peroxyl radicals, and hypochlorous and peroxynitrous acid. They can also chelate metal ions (*75*).

There are various methods for assessing the total antioxidant capacity of dietary fruits and vegetables. Among them are the equivalent antioxidant capacity assay (TEAC) using 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox), a hydrosoluble analogue of α-tocopherol, as reference (*93*), the ferric-reducing ability of plasma assay (FRAP) (*94*), and the widely used oxygen radical absorbance capacity assay (ORAC) (*95*). Halvorsen et al. (*68*) have measured the total antioxidant activity in a variety of dietary plants used worldwide by FRAP assay. They reported a large variation in their ability to reduce Fe^{3+} with a >1000-fold difference among total antioxidants in various dietary plants. Vegetables such as kale, chili pepper, red cabbage, parsley, artichoke, Brussels sprouts and spinach contained high antioxidants. Analyses of fruits demonstrated that pomegranate, grape, plum, pineapple, date, and kiwi have potent antioxidant activity (in decreasing order); most berries (e.g., various small fruits such as dog rose, crowberry, blueberry, strawberry, blackberry, raspberry) as well contained very high concentrations of antioxidants. Notably, most members of the citrus family (e.g., lemon, clementine, orange, grapefruit, and lime) also contained high amounts of antioxidants. However, the classification could differ from one assay to another. For instance, sulfur-containing compounds could not be detected by FRAP assay. Recently, Halvorsen and co-workers (*96*) analyzed the total concentration of redox active compounds in 1113 food samples obtained from the U.S. Department of Agriculture National Food and Nutrient Analysis Program. The antioxidant analysis was also based on the reduction of ferric ions using 2,4,6-tripyridyl-*s*-triazine (TPTZ). Of the 50 food products highest in antioxidant concentrations, 13 were spices, 8 were in the fruit and vegetable category, 5 were berries, 5 were chocolate-based, 5 were breakfast cereals, and 4 were nuts or seeds (**Table 4**). On the basis of typical serving sizes, blackberries, walnuts, strawberries, artichokes, cranberries, brewed coffee, raspberries, pecans, blueberries, ground cloves, grape juice, and unsweetened baking chocolate were at the top of the ranked list. Of the dried herbs tested, oregano, sage, peppermint, thyme, and lemon balm contained very high levels of antioxidants as did spices such as clove.

The evaluation of phenolic compounds in commercial fruit juices and fruit drinks revealed that purple grape juice contained the largest number of individual phenolic compounds and also the highest concentration of total phenolics (*97*). The main components were flavan-3-ols, anthocyanins, and hydroxycinnamates, which accounted for 93% of the total phenolic content. In contrast, white grape, pineapple, and tomato juices had the lowest total phenolic content. Interestingly, their antioxidant level was related to phenolic content (*97*). These data suggest that the consumption of fruit juices could have a positive impact on health. Recently, the Kame project indicated that long-term fruit juice consumption can provide protection against AD (*98*).

Table 4. 50 Foods with the Highest Antioxidant Contents per Serving Size [Modified from Halvorsen et al. (*68*)]

product	antioxidant content (mmol/100 g)
cloves, ground	125.549
oregano leaf, dried	40.299
ginger, ground	21.571
cinnamon, ground	17.647
turmeric powder	15.679
walnuts	13.126
basil leaf, dried	12.307
mustard seed, yellow, ground	10.527
curry powder	9.98
pecans	9.668
chocolate, baking, unsweetened	8.876
paprika	8.601
chili powder	8.372
parsley, dried	7.43
molasses, dark	4.9
pepper, black	4.444
artichokes, prepared	4.237
chocolate, dark	4.188
blackberries	3.99
whole-grain cereal	3.412
cranberries	3.289
pudding mix, chocolate, cook-and-serve	3.026
bran cereal	2.925
power bar, chocolate flavor	2.757
chocolates, sugar-free	2.567
raspberries	2.334
strawberries	2.159
blueberries	2.154
cabbage, red, cooked	2.153
wine, red	2.135
barley malt syrup, organic	2.121
prunes	2.018
cherries, sour	1.814
peppers, red, cooked	1.64
chocolate cookies with vanilla creme filling	1.604
Cocoa Krispies cereal	1.558
chocolate chip cookies	1.524
mustard, yellow, prepared	1.501
milk chocolate candy	1.483
pistachios	1.426
plums	1.33
kiwi fruit	1.325
corn flakes	1.255
coffee	1.249
spinach, frozen	1.226
flaxseed, ground or milled	1.125
rice and corn cereals	1.121
toasty peanut crackers	1.101
cupcakes, chocolate	1.059
grape juice	1.011

IV. POLYPHENOL INTAKE AND RISK OF DEMENTIA

Many epidemiological studies have documented the influence of dietary habits and antioxidants on the incidence of neurodegenerative disorders such as AD, but these analyses have yielded inconsistent results. For instance, the Honolulu−Asia Aging study, a longitudinal study of elderly Japanese-American men, examined the association between midlife dietary intake of antioxidants and the incidence of late-life dementia and its subtypes in 2459 men with a follow-up between 1991 and 1999. This analysis concluded that intakes of β-carotene, flavonoids, and vitamins E and C did not modify the risk of dementia (*99*). Flavonoid intake was estimated using mean intake of tea (green and black); information on wine drinking by type (red or white) was not available, but this is presumed to be a minor source of flavonoids in this population. Another limitation of this study is that nutrient intakes were determined from a single 24 h dietary recall that may not be representative of usual food consumption, in contrast to other studies such as the Rotterdam study in which dietary intake was estimated with a semiquantitative food frequency questionnaire. With a total of 5395

participants and a mean follow-up of 6 years, this analysis found that high intake of vitamins C and E may lower the risk of AD (*100*). A suggestion of a protective effect of vitamin E against AD was also reported in the Chicago Health and Aging Project after 3.9 years of follow-up (*101*). Interestingly, the protective association of vitamin E was observed only in persons who were ApoE4 negative. A protective association between flavonoid intake and dementia was found in the so-called PAQUID study, a 5- and 10-year follow-up study of a cluster sample of 1640 subjects in the southwestern departments of Gironde and Dordogne in France. This study suggested that an average intake of 14.3 ± 5.85 mg/day of dietary flavonoid was associated with less cognitive decline in subjects aged 65 years or older (*102*). The PAQUID study also showed that people drinking three to four glasses of wine per day had 80% decreased incidence of dementia and AD compared to those who drank less or did not drink at all (*103*). The consumption of fruit and vegetable juices containing high concentrations of polyphenols, at least three times per week, may play an important role in delaying the onset of AD, particularly in ApoE4 carriers (*98*). Recently, an association between Mediterranean diet (MeDi) and lower risk of AD has been reported. A case-control study nested within a community-based cohort (194 AD patients vs 1790 non-AD) in New York indicated that higher adherence to a Mediterranean diet was associated with lower risk for AD (*103, 104*). In addition, higher adherence to the MeDi is associated with lower mortality in AD (*105*). This diet consists of high amounts of fruits, vegetables, cereals, and fish, mild to moderate amounts of alcohol, and low amounts of red meat and dairy products. An increase of the consumption of fruits and vegetables is also associated with a reduced risk of stroke, a risk factor for AD. He and co-workers carried out a meta-analysis and found that individuals with more than five servings per day had a significantly reduced risk of stroke (*106*).

These clinical and epidemiological studies suggest that the consumption of flavonoids and polyphenols from fruits, vegetables, or beverages could reduce the risk of AD. However, the relationship between polyphenol consumption and risk of dementia needs further investigations. One of the limitations of most studies was that dietary assessement were collected closer to the onset of dementia (aged 65 years and more), once the oxidative stress level is already high and most neurons are degenerated, except for the Honolulu−Asia study, in which subjects were, on average, aged 52.4 ± 4.2 years. Numerous in vivo and in vitro studies performed in animal models or cell culture demonstrated that the antioxidant activity of phenolic compounds is unlikely to be the sole explanation for their protective cellular effects.

V. MECHANISMS OF ACTION OF DIFFERENT POLYPHENOLS

In the following paragraphs, we will review some mechanisms and targets of the most consumed polyphenols and particularly their beneficial effects against the Aβ-induced toxicity and their neuroprotective effects.

V.1. Green Tea Catechins. Green tea is rich in flavonoids (30% of dry weight of a leaf) (*107*), with the main compounds being epigallocatechin-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin (EC), and (−)-epicatechin-3-gallate (ECG) (**Figure 2**). Catechin intake has been associated with a wide variety of beneficial health effects (*108*). All of the catechins have a wide variety of biological actions pertaining to their chemical structure, but the different mechanisms underlying these actions have not been fully elucidated. Their antioxidants and free radical scavenging activities mainly contribute to their beneficial effects. These flavonoids have antioxidant potencies in the order of EGCG > ECG > EGC > EC (*109*). Their free radical scavenging abilities relate to the gallate moiety esterified at position 3 of the C ring, the catechol group (3,4-dihydroxyl groups) on the B ring, and the hydroxyl group at positions 5 and 7 on the A ring. The galloylated catechins are more active antioxidants due to their higher phospholipid/water partition coefficients (*110*). Moreover, the free radical scavenger property increases with the number of hydroxyl groups the catechin possesses. For instance, EGCG and EC possess eight and five hydroxyl groups, respectively, and the antioxidant activity of EGCG is higher than that of EC. Furthermore, their antioxidant abilities are higher than those of α-tocopherol or vitamins C and E.

Catechins can exert their antioxidant activity through various mechanisms, one being by chelating metal ions such as copper(II) and iron (II), and therefore prevent the generation of potentially damaging free radicals. Thus, reduction of the free iron pool by EGCG chelation may lead to the suppression of the translation of APP mRNA. Accordingly, Levites et al. have demonstrated that prolonged administration of EGCG to mice induced a reduction in holo-APP levels in the hippocampus (*135*). This result was supported by those obtained in cell culture models with a concomitant decrease in Aβ levels.

Catechins may also exert their antioxidant effects through the ultrarapid electron transfer to ROS-induced radical sites on DNA or by forming stable semiquinone free radicals. Moreover, after the oxidation of catechins by free radicals, a dimerized product is formed with an increased iron-chelating potential and ability to scavenge superoxide anions. The prevention of oxidative-induced damage by catechins is very effective as catechins can inhibit the ROS-induced damage by a wide variety of initiators including hydrogen peroxide, iron, paraquat, or radiolysis. Antioxidant properties of catechins were also observed in different in vivo models. For instance, rats receiving green tea extracts orally exhibited higher levels of antioxidant enzymes such as glutathione peroxidase and reductase, superoxide dismutase, and catalase (*111*). These effects on antioxidant levels were also investigated in human. It has been evidenced that after 42 days of the consumption of 2 cups of green tea, containing approximately 250 mg of total catechins, a significant increase in plasma total antioxidants was observed, whereas the plasma peroxide level decreased (*112*). Catechins also decreased oxidative stress by inhibiting the activity of xanthine oxidase (*113*), a ROS-generating system. Catechins can also protect lipids from oxidation in the liver, serum, and brain (*111*). For instance, it has been demonstrated that catechins could protect against lipid peroxidation induced by 6-hydroxydopamine, hydrogen peroxide, and iron (*114*). These antioxidant effects are observed in vitro with concentrations ranging from 1 to 50 μM. However, with higher concentrations (100−500 μM) and in the presence of copper(II) or iron(III), EGCG exacerbated oxidative stress, cytotoxicity, and DNA damage induced by hydrogen peroxide (*115–117*).

EGCG could also modulate apoptosis pathways to protect cells against oxidative stress. The effects of catechins on apoptotic pathways could be divergent. For instance, on PC12 cells EGCG, at low doses (1−10 μM), could inhibit caspase-3 activity or activate the PI3K/Akt pathway, which promote cell survival (*118*). On the other hand, catechins could also modulate apoptosis by altering the expression of anti-apoptotic and pro-apoptotic genes. In SH-SY5Y neuronal cells, EGCG prevented the expression of pro-apoptotic genes Bax and Bad while

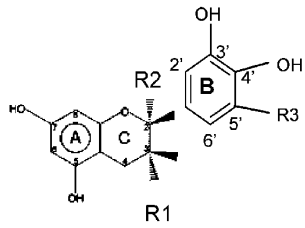
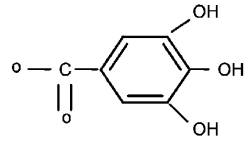
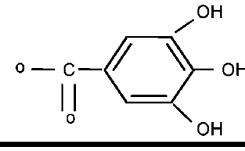
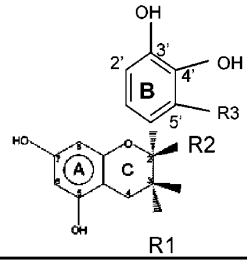
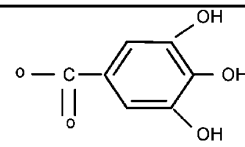
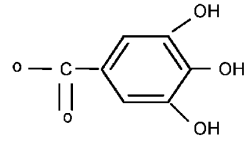
	R1	R2	R3
(+)-Catechin	OH	H	H
(+)-Gallocatechin	OH	H	OH
(+)-Catechin-gallate		H	H
(+)-Gallocatechin gallate		H	OH
	R1	R2	R3
(-)-Epicatechin	OH	H	H
(-)-Epigallocatechin	OH	H	OH
(-)-Epicatechin gallate		H	H
(-)-Epigallocatechin gallate		H	OH

Figure 2. Chemical structures of different catechins. Catechins have a three-ring structure with two or three hydroxyls on the B ring and with or without a gallate group at the C3 position of the C ring.

inducing the anti-apoptotic genes Bcl-2, Bcl-w, and Bcl-X in 6-hydroxydopamine-induced apoptosis (*119, 120*). EGCG promotes cell survival by restoring the protein kinase C activity, a critical regulator of cell proliferation and survival. However, at high doses, EGCG (50−500 μM) can induce pro-apoptotic properties by increasing Bax, Bad, and caspase-6 activity while decreasing Bcl-x and Bcl-2 activity.

There is substantial evidence that catechins can exert anti-inflammatory effects. This could be due to their abilities to scavenge NO, the peroxynitrite anion, or to reduce the activity of NO synthase (*121, 122*) with EGCG being the most effective (*123*). The neuronal nNOS and the inducible iNOS isoforms could also be inhibited by catechins (*124*). This effect of catechins likely involved the inhibition of the activation of the transcription factor NF-κB as the κB sequence is present in the promoter region of the iNOS gene (*125*). On the contrary, catechins could induce the endothelial isoform eNOS activity, a vasodilatator-inducing enzyme. This activity contributes to the anti-inflammatory effects of catechins (*126*). Another mechanism of action proposed may be the presence of the

antioxidant response element (ARE) on the promoter of the eNOS gene, and catechins could bind to the ARE and activate eNOS (*127*). These effects of EGCG on NOS activities also contribute to the anti-ischemic effect of EGCG (*108*). The anti-inflammatory effect of EGCG has also been studied in many cell types through the regulatory effect of EGCG on cytokine secretion. For instance, Kim et al. (*128*) have demonstrated that EGCG was able to inhibit the production of IL-1 and attenuate the expression of cyclooxygenase-2 induced by IL-1 and Aβ or the activation of NF-κB and MAPK pathways induced by IL-1 and Aβ (*128, 129*).

The prevention of cerebrovascular diseases or stroke by green tea has been evidenced during a 4-year follow-up study with 5910 individuals. The incidence of cerebral hemorrhage and stroke were 2-fold higher in those who consumed less than five cups than in those who consumed five cups or more daily (*130*). An inverse correlation between black tea consumption and the incidence of stroke was also replicated in a cohort of 552 men aged 50−69 years and followed up for 15 years (*131*). However, this inverse association was not observed in the Zutphen Study (*132*).

Although there is no significant outcome relative to tea consumption in AD case control, there are several in vitro studies showing that green tea extract may protect neurons from Aβ-induced damages (*133–136*). Over the past decade, intense focus has been placed on the processes of APP proteolysis and Aβ metabolism as possible targets for AD therapy. Various synthetic and naturally occurring compounds have been analyzed for their efficacy in the modulation of these pathological events. Among them, EGCG is able to regulate the proteolytic processing of APP both in vitro and in vivo (*134*). In neuronal cell cultures, it could promote the nonamyloidogenic α-secretase pathway (*134*). In primary neuronal cells derived from a transgenic mouse model overexpressing the human APP containing the AD-linked K670M/M671L double mutation (Swedish mutation), EGCG, at 20 μM, significantly reduced Aβ peptide generation (Aβ_{1-40} and Aβ_{1-42}) by 38%, with purified EGCG being more potent than green tea (*137*). These results were strengthened by experiments on N2a cells stably transfected with "Swedish" mutant APP, where EGCG treatment led to marked elevation in active α-desintegrin and metalloprotease (ADAM 10) proteins, ultimately leading to the nonamyloidogenic APP processing pathway (*138*).

Green tea catechins, especially ECGC, also reduced the activation of a number of signaling pathways such as p38 and JNK of MAPKs (*128*) and induce the phosphorylation of protein kinase C (*135, 139*) and phosphatidylinositol-3-kinase (PI-3 kinase)-Akt (*118*), and these modulations may mediate some of the neuroprotective effects of EGCG. Protein kinase C (*134, 135*) plays a central role in neuronal cell survival, and loss in its activity is frequently observed in neuronal insults such as in the presence of Aβ peptide accumulation and other neurotoxins (*140*). In neuronal cell lines and primary cells in culture, EGCG prevented the decline of ERK1/2 induced by 6-hydroxydopamine or by oxidized low-density lipoproteins (*135, 141*). MAPKs are also involved in the regulation of the expression of pro-apoptotic and anti-apoptotic genes. EGCG-treated SH-SY5Y neuroblastoma cells have decreased expression of the pro-apoptotic genes Bax, Bad, cell cycle inhibitor Gadd45, Fas ligand, and tumor necrosis factor-mediated apoptosis ligand TRAIL (*134, 142*).

All of the catechins are rapidly absorbed and widely distributed (*143*), and the peak concentration in plasma is reached 1.4−2.4 h after ingestion (*144*). For instance, Wistar rats exposed to epicatechin (oral gavage of 100 mg/kg/day) had steady-state plasma levels of about 5 μM for epicatechin and just over 1 μM for 3′-*O*-methylepicatechin, as well as almost 50 μM for glucuronidated epicatechin and 20 μM for glucuronidated 3- *O*-methylepicatechin (*77*). Very low concentrations of glucuronidated 4′-*O*-methylcatechin were also detected. LC-MS analysis demonstrated the presence of very small quantities of epicatechin, 3′-*O*-methylepicatechin, and the 5-*O*- and/or 7-*O*-glucuronides of epicatechin in the brain of these rats. It is likely that the glucuronides were formed in situ in neuronal cells, as they are considered to cross the BBB very poorly, and it is known that uridine diphosphate-glucuronyl transferase (UDP-GT) activity is present in the central nervous system of rats (*145*) and humans (*146*). For example, *cis*- and *trans*-resveratrol, polyphenolics found in wine, were 3-O-glucuronidated in rat brain tissue and rat astrocytes (*147*). Similar to the study with epicatechin, no B-ring 4′-*O*-glucuronide was found. The total concentration of epicatechin and metabolites was estimated to be about 0.4 nmol/g of brain tissue, but the investigators state that the concentrations were too low to quantify accurately (*148*). Some in vivo studies have shown that 0.33% of EGCG administration can reach the brain (*90*) and that frequent consumption of green tea enables the body to maintain a high level of catechins. Another study exposing rats to grape extract known to contain numerous polyphenolics including epicatechins also found no trace of epicatechins or its methylated and glucuronidated metabolites in brain (*149*). A study more relevant for human exposure to epicatechins followed six subjects (scheduled for lumbar puncture) after the ingestion of a 300 mL boiling water infusion of 7 g of green Kenyan tea (*150*). The average intake of (−)-epicatechins was 53 μmol of epicatechin, 149 μmol of epigallocatechin, 206 μmol of epigallocatechin-3-*O*-gallate, and 97 μmol of epicatechin-3-*O*-gallate. After 1 h, plasma levels of the epicatechins were readily detectable with total epicatechin concentrations amounting to about 1.6 μM; however, nothing was found in cerebral spinal fluid. Each 200 mL cup of green tea contains approximately 200 mg of catechins, with 88 mg of EGCG (*151*). However, the quantities of catechins are inconsistent with various brands and origins of green tea (*152*). This makes it difficult to know exactly the amount of green tea required daily to provide a neuroprotective effect.

In conclusion, in addition to their known antioxidant properties, catechins can target other pathways to exert their neuroprotective effect. These studies demonstrated that catechins could protect different cell types against various cytotoxic compounds independently of their free radical scavenger properties but through some emerging pathways that have attracted much attention recently (**Figure 3**). However, current epidemiological and clinical evidence correlating catchin intake and the incidence of AD is inconsistent. It is not clear whether epicatechins are capable of entering the brain in concentrations sufficiently high to be able to exert their beneficial effects.

V.2. Curcumin. Curcumin is a major chemical component of turmeric (*Curcuma longa*) and is used as a spice to give a specific flavor and yellow color to Indian curries and in food preservation. Interestingly, the prevalence of AD in people aged 70−79 years in India is 4.4-fold less than in the United States (*153*). Turmeric is derived from the rhizome, or root, of the plant. There is substantial in vitro evidence indicating that curcumin has antioxidant, anti-inflammatory, and antiamyloid activities (*154*). For instance, curcumin could inhibit lipid peroxidation (*155*), activate glutathione *S*-transferase (*156*), or induce heme oxygenase-1 (HO-1) (*157*). HO-1 induction occurs

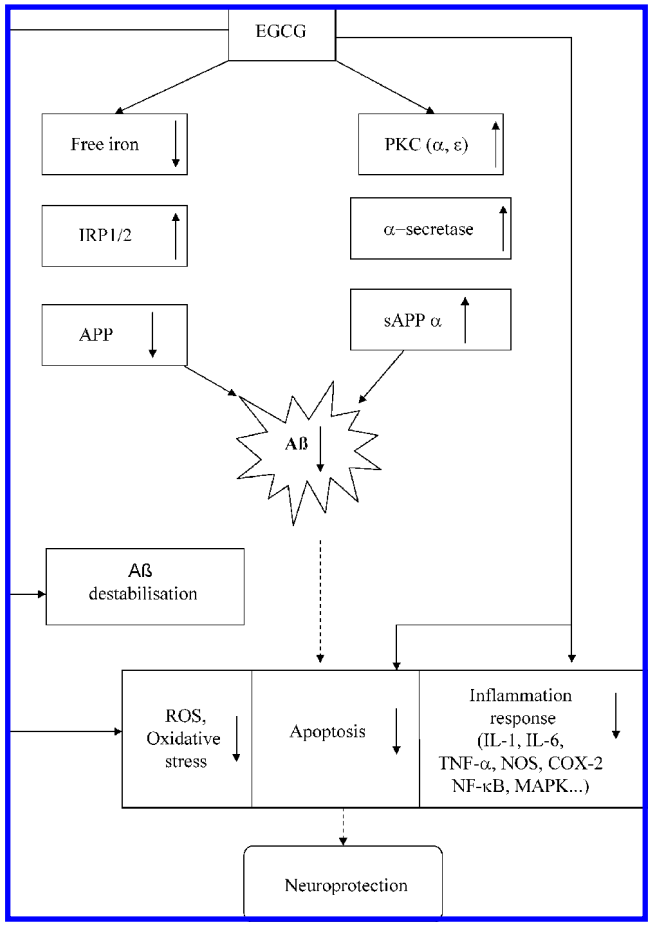


Figure 3. Potential pathways involved in the neuroprotective mechanisms of EGCG. Modified from Mandel et al. (*206*).

through the antioxidant response element (ARE) (*158*). Curcumin could also chelate the redox active metals iron (Fe^{2+}) and copper (Cu^{2+}) (*159*).

Inflammation is thought to be implicated in the pathophysiology of AD. Some epidemiological studies have consistently demonstrated an association between the use of nonsteroidal anti-inflammatory drugs and a subsequent decreased risk of the development of AD (*160–162*). Curcumin has been shown to have anti-inflammatory effects as it is a good inhibitor of lipoxygenase and COX-2 (*163, 164*), both enzymes being responsible for the synthesis of the pro-inflammatory leukotrienes, prostaglandins, and thromboxanes. Curcumin is also a suppressor of iNOS and a potent inhibitor of NF-κB and AP-1 activation (*165–167*). This mechanism is likely involved in the inhibition of the expression of inflammatory cytokines COX-2 and iNOS, as these transcription factors are well-known to regulate these inflammatory factors. All of these factors (IL-1, TNFα, COX-2, iNOS, JNK, NF-κB) are also implicated in Aβ toxicity.

Aggregation of Aβ into fibrils and the subsequent formation of amyloid plaques are crucial steps in the pathogenesis of AD. It has been found that curcumin inhibits the formation and extension of Aβ fibrils and destabilizes preformed Aβ fibrils in a dose-dependent fashion between 0.1 and 1 μM (*168*). Curcumin could also bind to fibrillar Aβ regardless of the specific Aβ sequence.

In light of the spectrum of activities, curcumin represents a hopeful approach for delaying or preventing the progression of AD. Therefore, the effects of curcumin have been tested in several animal models for AD. When fed to aged Tg2576 mice with advanced amyloid accumulation, curcumin reduced Aβ levels and plaques (*169*). In this study, low (160 ppm) and high doses (5000 ppm) of curcumin significantly lowered oxidized proteins and IL-1β, whereas low doses reduced plaque burden. Subsequent in vivo studies using multiphoton microscopy demonstrated that curcumin could cross the BBB, targeting senile plaques in Tg2576 mice and disrupting existing plaques (*170*).

However, preclinical data from animal models and phase I clinical studies performed with human volunteers and patients have demonstrated low systemic bioavailability following oral intake. The absorption, distribution, metabolism, and excretion of curcumin in rodents has been widely described. These studies support the notion that curcumin undergoes a rapid and efficient metabolism that severely curtains its availability. An ingested dose (1 g/kg) administered to rats resulted in about 75% of the spice's metabolites being detected in feces (*171*). Intestinal metabolism, particularly glucuronidation and sulfation, of curcumin might explain its poor systemic availability (*172*). The metabolites were characterized mainly as glucuronides of tetrahydrocurcumin and hexahydrocurcumin.

Altogether, curcumin, a highly lipophilic compound, can protect cells against Aβ toxicity by preventing Aβ peptide aggregation and reducing plaque burden, through its antioxidant and anti-inflammatory activities and the inhibition of cell signaling pathways at multiple levels. However, curcumin undergoes rapid metabolism, and the bioavailability of the parent compound is low (*172*). Therefore, more investigations are necessary on curcumin or on related compounds to gather more information on biomarkers of AD pathology in addition to clinical trials data.

V.3. Resveratrol. Resveratrol is a non-flavonoid polyphenolic found in grapes, red wine, and berries. The concentration of resveratrol in red wine is in the range of 1.5−3 mg/L (*173*). There are two isomeric forms of resveratrol, the biologically inactive *cis*-resveratrol and the most biologically active *trans*-resveratrol (*trans*-3,4,5-trihydroxystilbene). This compound has been the focus of a number of studies demonstrating its antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic effects (*173–175*). Interestingly, several epidemiological studies indicate an inverse correlation of wine consumption and incidence of AD (*176–178*).

In several in vitro studies, resveratrol has been recognized for its powerful antioxidant properties. At the cellular level, resveratrol could protect PC12 cells against Aβ-induced toxicity and prevent the accumulation of intracellular ROS (*179*). Resveratrol can also protect SH-SY5Y neuroblastoma cells and primary hippocampal neuronal/glial cells from H_2O_2, NO, and Aβ-induced toxicity (*139, 180–182*). In cultured PC12 cells, resveratrol also increased the HO-1 activity, and similarly in cortical mouse neurons an up-regulation of HO-1 gene expression via the activation of NF-E2-related factors 2 (NRf2) (*183*) was observed (*184*). Interestingly, resveratrol exhibited its neuroprotective effects when it was used in pretreatment, in cotreatment, or in post-treatment.

The inhibition of Aβ secretion by resveratrol could also be implicated in this neuroprotective effect because the secretion of Aβ is reduced in two cell lines, HEK 293 and N2a, transfected with APP695 (*185*). This effect was not mediated by β- and γ-secretase activities but may be through the elevation of the degradation of Aβ peptide. However, resveratrol did not affect Aβ-degrading enzymes such as neprilysin, endothelin-converting enzyme-1 or -2, and insulin-degrading enzyme (*185*).

It is well-known that reducing food intake or caloric restriction extends lifespan in a wide range of species. Recently, it has been found that resveratrol can mimic dietary restriction and trigger sirtuin proteins (*186*). The sirtuin enzymes are a phylogenetically conserved family of enzymes that catalyze NAD-dependent protein deacetylation. In yeast, sir2 is essential for lifespan extension by caloric restriction and a variety of other stresses, including increased temperature, amino acid restriction, and osmotic shock (*70, 187*). Activators of sirtuins can be a key to extending lifespan and overcoming a variety of stresses in higher organisms. Among 18 small molecules that can increase human sirt1 activity, resveratrol induced the highest activity of sirt1 and increased the lifespan of yeast by nearly 70% (*188*). Analysis of the structure−activity relationship suggests that the hydroxylated *trans*-stilbene ring structure is essential for activation of sirt1. However, the mechanisms that link resveratrol to the activation of sirt1 and the subsequent protection of neurons against Aβ remain unknown. Nevertheless, resveratrol-induced sirt1 has been found to repress p53 activity and to suppress apoptotic activities of FOXO proteins, thereby protecting neurons against apoptosis-induced by Aβ.

The NF-κB pathway is also a target of resveratrol. In a recent study with mixed neuron/glial cultures from Sprague−Dawley rat, it has been demonstrated that resveratrol—by inducing sirt1 activation—could inhibit the NF-κB signaling in microglia and astrocytes with a neuroprotective effect against Aβ-induced toxicity (*183*). NF-κB signaling controls the expression of both iNOS and cathepsin B, two factors that mediate apoptosis. In PC12 cells, Aβ induces the degradation of IκBα, the inhibitory subunit of NF-κB activation, and increases the nuclear translocation of p65. The activation of NF-κB was reversed when cells were treated with resveratrol (25 μM) (*189*). We have recently demonstrated that sirt1 could be activated by flavonoids and that this activation is associated with the NF-κB inhibition and protection against Aβ toxicity (*65*). Thus, modulation of different sirtuins by phenolic compounds could provide an important arsenal to overcome variety of stresses that compromise neuronal survival in different neurodegenerative diseases such as AD.

After oral administration of resveratrol, it is rapidly metabolized (within 2 h, with a peak in <30 min) to glucuronide acid and sulfate conjugates in the liver and intestinal cells (*173*). More than 90% of total resveratrol, given as pure aglycone, circulates in the plasma in the conjugated form, and glucuronidation predominates the metabolism of resveratrol. These results indicate that the circulating forms of resveratrol are predominantly modified metabolites and not the original aglycone. Therefore, the antioxidant and anti-inflammatory activities and the effect on cell signaling of the original aglycone compound seem to be considerably diminished due to its extensive and rapid metabolism. However, the biological activities of the circulating form and their functions remain to be determined, particularly their implication in neuroprotective effects. Indeed, resveratrol appears to reach the brain as was shown in one rat study exposing 250 g males to 50 mg/kg [^{3}H]-*trans*-resveratrol by oral gavage (*77*). The concentrations found in the whole brain after 2 and 18 h were about 0.03 and 0.01%, respectively, of the original dose, suggesting that distribution to the brain is minimal.

In summary, it is clear that the neuroprotective effect of resveratrol implicates different pathways which may be critical to neuronal protection in AD. In addition to its antioxidant effects, the efficacy of resveratrol against Aβ toxicity also involves several transduction pathways or the modulation of glia/astrocyte functions. All of these functions may play synergistic roles in treating AD. However, pharmacokinetic studies indicate that resveratrol is rapidly metabolized in liver and intestinal epithelials cells. Therefore, the efficacy of resveratrol in the treatment of AD will also depend on the bioavailability of its metabolites and their biological activities.

V.4. Effects of Polyphenols from Berries and Pomegranate on Cognitive Performance. Berries are rich sources of phenolic compounds such as phenolic acids as well as anthocyanins, proanthocyanidins, and other flavonoids (e.g., ellagitannins). The content of phenolics in berries is affected by the degree of maturity at harvest, by the cultivar, and by the pre- and postharvest environnments. For instance, the total phenolic acid content ranged from 2845 to 5418 mg/kg (*190*) with hydroxycinnamic acids constituting from 68.9 to 85% of the total; more than 20 phenolic acids could be identified in berries. In blueberries (*Vaccinium ashei reade*), catechin is the major flavonoid, reaching 387 mg/100 g of fresh weight; epicatechin concentrations ranged from 34 to 129 mg/100 g of fresh weight, and total anthocyanins ranged from 84 to 113 mg/100 g of fresh weight (*191*). It has been estimated that 1.20 g of total anthocyanins was present in human serum after a consumption of 100 g of blueberries, and maximal level was reached 4 h after the consumption. Interestingly, a significant positive correlation between serum anthocyanin content and postprandial antioxidant status has been observed (*192*). This absorption could have some positive effects in the brain through several processes, as has been demonstrated in various animal studies. Dietary supplementation for 8 weeks with blueberry extracts reversed cognitive deficits in Morris water maze performance test in 19-month-old rats (*193*). However, the effect of blueberry extracts on cognitive functions might involve more than just their antioxidant actions. For example, aged rats on a blueberry extract diet had significantly lower levels of NF-κB than aged rats on a control diet (*194*). It has been described that the aged rat control diet group had significantly higher average NF-κB levels than young rats (*194*). These results are in accordance with the known effect of flavonoids on cell signaling such as on the activity of NF-κB (*65, 195*). Additional evidence was seen in a recent study with the double-transgenic mice model of AD overexpressing APP and presenilin 1, in which genetic mutations promote the production of the Aβ peptide and the hallmark of AD-like senile plaques in several regions. When these mice were supplemented with blueberry extract (2% of diet) at 4 months and continued until 12 months of age, their performance in a Y-maze cognitive performance test was similar to that of nontransgenic mice and significantly better than that of nonsupplemented transgenic mice (*196*). However, examination of the brains of these mice revealed that supplementation of blueberry extract did not affect the Aβ peptide production or deposition or the number of plaques. These data suggest that the impairment of cognitive functions observed in these transgenic mice may not necessarily be the result of deposition of the Aβ peptide. In these mice supplemented with blueberry extract, the concentrations of hippocampal ERK as well as striatal and hippocampal PKCα were higher than in transgenic mice supplemented with control diet. Both protein kinase C and ERK have been shown to be involved in early and late stages of memory formation (*197*). These results indicate that blueberry extract supplementation might prevent cognitive and motor deficits through various neuronal signaling pathways. Furthermore, short-term blueberry supplementation increases hippocampal plasticity (*198*). Diet supplemented with blueberry extract could also protect the brain against apoptosis as rats receiving

blueberry extracts had significantly lower caspase-3 activity in the ischemic hemisphere (*199*). Taken together, these studies demonstrate that blueberry extract-supplemented diets could protect neuronal loss and prevent the decrease of cognitive functions against various insults through antioxidant, anti-apoptotic, and regulation of cell signaling mechanisms.

Pomegranates (*Punica granatum* L.) contain very high levels of polyphenols compared with other fruits and vegetables (*200–202*), and the most important polyphenols are ellagic acid, punicalagin, and hydrolyzable tannins such as ellagitannins and gallotannins.

Recently, the administration of pomegranate juice (PJ) to Tg2576 transgenic mice expressing the APP695 human gene from 6 to 12.5 months of age exhibited improvements in cued and spatial learning tasks as compared to a sugar water control group (*203*). Additionally, PJ-treated mice had a significantly reduced burden of plaque load and soluble $A\beta_{1-42}$ in the hippocampus. Grape juice is also a rich source of flavonoids that include catechins, epicathechins, quercetin, anthocyanins, and proanthocyanidins (*3*). When aged Fisher 344 rats were given 10 or 50% of grape juice from 19 to 21 months of age, their performance motor functions in rod walk and cognitive performance on the Morris water maze were improved (*204*).

Several dietary supplements with either spinach or strawberry extracts have also been reported to reduce some neurological deficits in aged animal models (*113, 199*).

VI. CHALLENGES FOR RESEARCH ON POLYPHENOLS IN NEURODEGENERATIVE DISEASES

Hundreds of polyphenols with potent antioxidant activity have been shown to have neuroprotective effects in vitro and in animal studies, but only a few compounds, for example, curcumin, have progressed successfully into active clinical trials in neurodegenerative diseases. Most reports on the beneficial effects of polyphenols are based on in vitro and in vivo studies either in cell cultures or in animal models, where there is not extensive neuronal damage. On the contrary, in human clinical trials, the patients already suffer from extensive neuronal loss and damage. Therefore, the important question arises whether polyphenols should be tested for therapeutic efficacy or as agents that can further slow the progression of disease. Second, few studies are available to conclusively prove that polyphenols can cross the BBB to exert their protective effects. More data and studies are required to validate that polyphenols can cross the BBB in sufficient quantity to exert their biological and pharmacological actions. Because most of the neurodegenerative diseases require a lengthy incubation time before clinical manifestation, it is worthwhile to conduct epidemiological studies regarding polyphenol intake and progression of diseases. In this regard the variation between geographical distributions of various neurological disorders should be compared with food polyphenolic composition data across various countries and ethnicities. These data could throw light on why AD is more prevalent in certain regions and its correlation with local dietary habits, especially with regard to polyphenol intake. Another aspect of polyphenols that warrants further detailed investigation is synergistic and antagonistic activities in combination with other biological antioxidants. For example, ascorbate and catechin have been shown to have a synergistic effect as ascorbate could protect catechin from oxidation (*205*), leading to the hypothesis that polyphenol antioxidants may be part of a broader antioxidant network of the organism. Another rapidly developing aspect of free radicals research is their participation in the process of mediating and regulating cellular functions without causing unwarranted oxidative stress. It may be possible that dietary polyphenols continuously participate in the regulation of cellular functions independent of their antioxidant properties. In addition, we cannot exclude the possibility that polyphenolic compounds may regulate the expression of some genes coding for antioxidant enzymes and thus help the neural cells to cope with increased oxidative stress.

VII. CONCLUSIONS

Polyphenols from fruits and vegetables seem to be invaluable potential agents in neuroprotection by virtue of their ability to influence and modulate several cellular processes such as signaling, proliferation, apoptosis, redox balance, and differentiation. Although abundant in fruits, vegetables, tea, wine, and medicinal plants, more detailed studies are required to determine their absorption, bioavailibity, and ability to cross the BBB. Their neuroprotective activity in various models of neurodegenerative diseases in vitro and in vivo have been documented, but it would be unwise to extrapolate these results to the human situation without proper clinical trials in patients suffering from irreversible and extensive neuronal loss. In addition, most cell culture or animal studies have been conducted on a short-term basis. Therefore, more long-term studies should be undertaken to determine their beneficial effects in slowly developing neurodegenerative disorders such as AD. In view of their multiple biological activities, polyphenols hold great promise as potential therapeutic/prophylactic agents in neurodegenerative diseases. Further studies are also required to understand the effect of ROS on basic cellular and molecular functions of the various nerve cells in the brain and how this in turn affects the physiopathology of neurodegenerative diseases. Also, the impact of ROS on the production of different neurotrophins, neurotransmitters, and steroids (glucocorticoids) in the brain and their possible modulation by polyphenols is worth examining as it will open up new vistas for the treatment of neurodegenerative diseases.

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Received for review November 30, 2007. Revised manuscript received February 18, 2008. Accepted March 5, 2008.

JF0735073