Antioxidant Plant Polyphenols and Cognitive Disorders

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Abbreviations

AD	Alzheimer's disease
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
BMI	Body mass index
CSF	Cerebrospinal fluid
ERK1/2	Extracellular signal-regulated protein kinases 1 and 2
FFQ	Food frequency questionnaire
GPX	Glutathione peroxidase
GSH	Reduced glutathione
GSSG	Oxidized glutathione
H_2O_2	Hydrogen peroxide
HIF1α	Hypoxia inducible factor 1α
LRP1	Low-density lipoprotein receptor-related protein1
MAP kinase	Mitogen-activated protein kinase
MCI	Mild cognitive impairment
MDA	Malondialdehyde
MMSE	Mini–mental state examination

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NADPH	Nicotinamide adenine dinucleotide phosphate
PI3 kinase	Phosphoinositide 3-kinase
PKC	Protein kinase C
PS-1	Presenilin-1
PUFAs	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SOD	Superoxide dismutase

1 Introduction

Numerous clinical and experimental data prove the role of oxidative stress in the development and progression of variety of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease, and other causes of cognitive disorders and dementia. Although, currently there is no efficient method to stop progression or cure neurodegenerative diseases, diet rich in plant polyphenols seems to decrease the risk of dementia and to slow down the rate of age-related decline in cognitive performance. There are thousands of polyphenols found in nature, and majority of them occur in flowering plants, their vegetative organs, flowers, and fruits. A group of polyphenols, called flavonoids, is found in significant levels in fruits and vegetables. On the basis of the oxidation state of the central pyran ring, flavonoids could be divided into 6 subclasses: flavonols (e.g., quercetin), flavones (e.g., apigenin), flavanones (e.g., hesperidin), isoflavones (e.g., genistein), anthocyanidins (e.g., cyanidin, pelargonin, malvidin), and flavanols (e.g., catechin, epicatechin, epigallocatechin). Phenolic acids (e.g., gallic acid, hydroxycinnamic acids) and stilbenes (e.g., resveratrol) belong to the nonflavonoid group of plant phenolic compounds. Almost all phenolic acids are present in plants as esters of glucose, tartaric acids, and quinic acid. Chlorogenic acid present in coffee and tea is an ester of caffeic acid and quinic acid. Due to presence of catechol ring, conjugated double bonds, and numerous hydroxyl substitutions in the backbone structure, plant polyphenols have distinct antioxidant activity. Therefore, researches initially focused on the investigation of this activity and its significance for human health in experimental and clinical studies. However, recent data revealed that plant polyphenols and their in vivo metabolites can evoke more complicated and specific effects than direct scavenging of reactive oxygen species (ROS).

They can influence cell functions including neurons in the brain via modulation of kinase-dependent intracellular signals transduction pathways. Moreover, polyphenols in transgenic animal models of Alzheimer's disease (AD)-like pathology decreased amyloid deposition in the brain and improved animals' behavior performance. These are in accordance with the results of observational (cross-sectional, longitudinal) and interventional studies (randomized, double-blind, placebo-controlled) in older humans showing positive effect of increased polyphenols dietary intake on cognitive performance.

2 Plant Polyphenols

2.1 Antioxidant Properties of Plant Polyphenols

Antioxidant activity was the earliest discovered characteristic of plant polyphenols. This topic was extensively studied in in vitro and in vivo models using selected biomolecules sensitive to oxidative damage, subcellular fractions, a variety of isolated cell suspensions and cell cultures, and laboratory animals as well as in clinical trials. These studies were executed with chosen purified polyphenols and polyphenols extract from various fruits, flowers, leaves, seeds, and other parts of plants. Consequently, hundreds of original papers describing antioxidant effects of plant polyphenols on prevention of cancer and cardiovascular and neurodegenerative diseases have been published so far. Since these issues have recently been largely reviewed and discussed elsewhere (Williams and Spencer 2012; Ebrahimi and Schluesener 2012; Vauzour 2012; Hu 2011; Choi et al. 2012; Bubols et al. 2013), this section will describe plant polyphenols antioxidant activity in a concise way.

Plant polyphenols can act as antioxidant by direct reaction with ROS and indirectly by stimulating natural processes that enhance cellular resistance to oxidative stress. Due to various substitutions in the backbone structure (especially the presence of hydroxyl groups), polyphenols can react and inactivate numerous free radicals and oxidants including superoxide, hydroxyl, peroxyl, lipid free- and carbon-centered radicals as well as singlet oxygen, nitric oxide, and peroxynitrite.

Polyphenols can also act as chelators of transition metal ions Fe^{2+}, Fe^{3+}, and Cu^{2+} that are involved in the conversion of hydrogen peroxide into hydroxyl radicals and stimulation of lipid peroxidation. This activity is attributed to the presence of o-diphenolic groups in the 3O, 4O-dihydroxy positions in the B ring and the keto structure 4-keto, 3-hydroxy or 4-keto, and 5-hydroxy in the C ring of flavonoid backbone (Thompson et al. 1976; Rice-Evans et al. 1996; van Acker et al. 1996).

On the other hand, the antioxidant activity of selected plant polyphenols and their metabolites expressed as the ability to reduce Fe^{3+} ions (FRAP) in vitro was positively associated with the presence of a catechol structure in the compound molecule. In addition, an aliphatic substitute at a catechol ring and a double bond in an aliphatic substitute conjugated with an aromatic ring of catechol contributed to almost 40 % of the variance in the FRAP of compounds with catechol in the backbone structure (deGraft-Johnson et al. 2007). Indirect antioxidant activity of polyphenols involves stimulation of synthesis of various enzymes that increase cellular resistance to ROS. For instance, intraperitoneal injection of green tea polyphenols (epigallocatechin gallate) increased the activity of two important antioxidant enzymes, catalase and superoxide dismutase, in mouse striatum (Levites et al. 2001). Insufficient supply of blood to the brain leading to local nervous tissue hypoxia is one of the causes of cognitive impairment and dementia. Some polyphenols (catechins, epigallocatechin gallate, resveratrol) present in red wine and green tea can increase synthesis of hypoxia-inducible factor 1α subunit (HIF1α) that normally rises under hypoxic conditions and activates genes encoding proteins involved in cell survival, angiogenesis, glycolysis, and iron metabolism. Thus, these polyphenols as

factors influencing activity of HIF1α and stimulating increased activity of antioxidant enzymes would express neuroprotective activity. Consequently, polyphenols revealed a significant protective effect against neurotoxicity and neurodegeneration induced by variety of factors (e.g., homocysteine, glutamate, kainic acid, *N*-methyl-D-asparate, glucose oxidase, bacterial endotoxin, transient global cerebral ischemia) under conditions of in vitro and in vivo models.

2.2 *Anti-Inflammatory and Other Biological Activities of Plant Polyphenols*

Since ROS belong to mediators of inflammation, any polyphenolic compound with distinct antioxidant activity will also have some anti-inflammatory properties. However, detailed molecular studies revealed that more specific mechanisms contribute to inhibitory effect of polyphenols on inflammatory processes including neuroinflammation. This issue was also extensively reviewed elsewhere (Williams and Spencer 2012; Ebrahimi and Schluesener 2012; Vauzour 2012). Therefore, only the main known mechanisms leading to anti-inflammatory effect of polyphenols in cerebral tissue will be listed below.

Polyphenols (especially flavonoids) can affect neuronal and glial functions via binding to various receptors including adenosine, nicotinic, estrogen, testosterone, or δ-opioid receptors.

Flavonoid-induced receptors stimulation can cause changes in the activation state of the mitogen-activated protein (MAP) kinase (e.g., naringenin), the phosphoinositide 3- (PI3) kinase (e.g., curcumin), the nuclear factor-κB (e.g., resveratrol, epigallocatechin gallate), and protein kinase C (PKC) pathways (e.g., resveratrol). These signal transduction pathways are involved in cell differentiation and apoptosis, cell survival (apoptosis inhibition), inflammatory response and also learning and memory, and reduction of amyloid plaque formation, respectively. Polyphenols can also inhibit activation of the glial cells (resident macrophages of the brain) and thus decreasing their ability to produce pro-inflammatory cytokines (TNF-α, IL-1β) and release superoxide radicals, hydrogen peroxide, and nitric oxide.

Polyphenol-induced improvement of cerebral blood flow via stimulation of nitric oxide production in the endothelium and inhibition of platelet aggregation may be an additional important mechanism of neuroprotection. All these effects will lead to suppression of oxidative stress and inflammatory response in the cerebral tissue and reduced risk of damage to neurons and their degeneration.

2.3 *Dietary Intake and Absorption of Polyphenols*

Since beneficial effect of fruits and vegetables consumption on the risk of chronic degenerative processes is attributed to various plant polyphenols which possess variety of biological activities, it is necessary to know which food products contain

the highest content of these compounds and how they are absorbed from the gut into the blood stream. Dietary intake of plant polyphenols depends on the types and amount of plant foods consumed and was estimated to be between 150 mg and 1 g (Aura 2008). Currently, there are hundreds and thousands of plant food products with different phenolic composition available for consumption on the market. Therefore, this subsection will focus only on those polyphenolics or plant products containing them that were tested in animal models of AD-like pathology and clinical trials involving humans with various levels of cognitive impairment and dementia (described in further subsections). Table 1 lists these polyphenolics and their nutritional sources as well as their main metabolites in the human body.

Table 1 Phenolic compounds, their nutritional sources, and main metabolites detected in human body that were tested in animals models of AD-like pathology and clinical trials involving humans with various levels of cognitive impairment and dementia

Phenolic compound	Nutritional source	Main metabolite in human[a]
Catechin and epicatechin	Green and black tea, red wine, chocolate, grape seed	3-(3-hydroxyphenyl) propionic acid,
Ellagic acid and ellagitannins	Pomegranate, raspberry, strawberry, nuts	Urolithins A and B
Gallic acid	Red wine, black tea, pomegranate, blackberry	4-O-methylgallic acid
Caffeic acid	Grapes, apples, blueberries, broccoli, coffee, red wine,	Acids: 3- and 4-coumaric, 3-(3,4dihydroxyphenyl)propionic, 3-(3-hydroxyphenyl)propionic, 3-hydroxybenzoic, 3-hydroxyhippuric, hippuric
Tannic acid	Tea, grapes,	4-O-methylgallic acid, pyrogallol, resorcinol[b]
Chlorogenic acid	Blueberries, coffee, tea, sunflower seeds	Acids: hippuric, ferulic, caffeic
Quercetin	Apples, onions, tea, blackcurrant	Acids: 2-(3,4-dihydroxyphenyl)acetic, 2-(3-hydroxyphenyl)acetic, 2-(3-methoxy-4-hydroxyphenyl) acetic
Epigallocatechin gallate	Green tea	5-(3′,4′-dihydroxyphenyl)-c-valerolactone, 5-(3′,5′-dihydroxyphenyl)-c-valerolactone, 5-(3′,4′,5′-trihydroxyphenyl)-c-valerolactone
Hesperidin	Orange juice	Eriodictyol, homoeriodictyol[b]
Proanthocyanidins (oligomers of catechin or epicatechin)	Apples, grapes, wine, tea, chocolate, cranberry	Acids: 3-(3-hydroxyphenyl) propionic, 2-(4-hydroxyphenyl)acetic, 3-(4-hydroxyphenyl)propionic, 3-(3-hydroxyphenyl)propionic, 3-(3-hydroxyphenyl)acetic, 3-phenylpropionic
Anthocyanins[c]	Red fruits, red berries, red wine	Acids: 3,4-dihydroxybenzoic, 3-methoxy-4 hydroxybenzoic, 4-hydroxybenzoic acid, 3,4-dimethoxybenzoic[d]

Based on Aura (2008), D'Archivio et al. (2007), Olthof et al. (2003), Stalmach et al. (2009), Shahrzad and Bitsch (1998), Nakamura et al. (2003), and Jin et al. (2010)

[a]Results obtained from analysis of human plasma, urine, feces, and experiments with human fecal microbiota

[b]Results obtained from experiments on rats

[c]Glycosides of anthocyanidins

[d]Depending on specific anthocyanin

Majority of dietary polyphenols exists as esters, glycosides or polymers that cannot be absorbed in the native form (D'Archivio et al. 2007) They must undergo the reaction of hydrolysis catalyzed by intestinal enzymes (e.g., β-glucosidase, lactase-phlorizin hydrolase) or enzymes produced by colonic microbiota. However, there are exceptions to this rule: quercetin glucosilation facilitates its absorption. Thus, quercetin glucosides absorption is more efficient than that of the aglycone itself and its subsequent hydrolysis catalyzed by cytosolic β-glucosidase takes place in enterocytes.

Those polyphenols that are not absorbed in the small intestine reach the colon where they could be transformed into less complex compounds by gut microflora before transportation into the blood. Thus, the combination of consumed polyphenols may differ to great extent from that absorbed and reaching tissues with circulating blood (Aura 2008). Further metabolism in enterocytes and liver (reactions of methylation, sulfation and glucuronidation) can also contribute to this difference and may affect the bioavailability of dietary phenolics (Aura 2008; Silberberg et al. 2006). These are supported by clinical experiments with dietary supplementation with chlorogenic acid. In subjects with intact colon, about half of ingested chlorogenic acid was metabolized to hippuric acid; however, in ileostomy subjects (without colon due to a total colectomy in the course of ulcerative colitis or polyposis coli), only traces of hippuric acid were detected in the urine (Olthof et al. 2003). There is a great interindividual variability in polyphenol bioconversion by colonic microbiota in healthy subjects. For instance, bioconversion of polyphenols from black tea and a mixture of red wine and grape juice differed in metabolite pattern, kinetics, and concentrations of specific products (Gross et al. 2010).

Shifts in the composition of resident bacteria can occur in response to numerous factors including changes of the diet, diarrhea, or antibiotic treatment. Thus, even the same subject can present altered polyphenols bioconversion in the colon at different time points. Therefore, it is very difficult to detect all the metabolites and evaluate their biological activity as well as to transfer results of in vitro experiments and on animal models into human physiology and medicine. In addition, these observations suggest different healthful effects obtained with the same polyphenols supplementation between various subjects.

2.4 Polyphenols Penetration to Brain Tissue

To answer the question as to why plant polyphenols can protect the brain from peroxidative damage and other neurodegenerative processes, it is necessary to know whether and how they can cross the blood–brain barrier and what determines their concentration in the brain structures. The knowledge about concentrations of specific polyphenols in the central nervous system would be helpful for the statement whether observed in vitro protective effects of polyphenols could be relevant to clinical practice. Although this problem is not completely solved, the results obtained so far seem interesting and promising for future clinical trials on efficacy

of plant polyphenols in protection from neurodegenerative disorders and decline of cognitive performance.

Single oral administration of $_{14}$C-labeled grape polyphenols preparation in rats resulted in the appearance of radioactivity in cerebral interstitial fluid sampled with microdialysis probes from hippocampus and also in brain slices obtained at 24-h post-dose (Janle et al. 2010). Maximal signals for labeled catechin/epicatechin (monomers, oligomers) peonidins, cyanidins, and cyanidin glycosides occurred in cerebral fluid sampled between 0.75 and 1.5 h after grape polyphenols ingestion. However, these signals were lower than those in corresponding samples of blood. The amount of residual label in the brain did not exceeded 1.7 % of the dose, and the radioactivity was spread homogenously over all the brain structures (Janle et al. 2010).

It is interesting that repeated oral administration of plant polyphenols in rats can increase their brain bioavailability. Single administration of increasing doses of grape seed polyphenolic extract (from 50 to 150 mg/kg body weight) resulted in the dose-dependent increase of plasma circulating gallic acid, catechin, epicatechin, and some of their metabolites; however, they were not detectable in the brain tissue (Ferruzzi et al. 2009). Repeated daily ingestion of grape seed polyphenolic extract for 10 days increased both plasma and brain bioavailability of gallic acid, catechin, and epicatechin with brain concentrations of these two latter compounds reaching about 570 and 290 pg/g of tissue (Ferruzzi et al. 2009). Thus regular prolonged ingestion of plant polyphenols may enhance their deposition in the brain structures and subsequently increase protective activity.

Dietary supplementation with blueberry extract (20 g of extract per kg of diet) for 8–10 weeks also resulted in the appearance of several blueberry anthocyanins (e.g., cyanidin-3-O-b-galactoside, peonidin-3-O-b-arabinoside, malvidin-3-O-b-galactoside) in the brain (cerebellum, cortex, hippocampus, striatum) of rats (Andres-Lacueva et al. 2005). The brain cortex showed the greatest number of detected compounds ($n=8$). Negative readings were obtained for brain samples from control animals without supplementation (Andres-Lacueva et al. 2005). Similarly, HPLC analysis revealed several anthocyanins (total concentration of 0.25 nmol/g of tissue) in the brain of rats fed with blackberry anthocyanin-enriched diet (15 g blackberry extract per kg of diet) for 15 days (Talavéra et al. 2005).

On the other hand, it should be pointed out that green tea polyphenols were able to reduce the elevated blood–brain barrier permeability in the rat model of experimental cerebral ischemia induced by middle cerebral artery occlusion (Zhang et al. 2010). Reduced expression of caveolin-1 and phosphorylated extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) is the suggested mechanism by which these polyphenols can improve the function of blood–brain barrier (Zhang et al. 2010).

Putting together these results, it is clearly visible that diet supplementation with grape, blueberry, or blackberry extracts results in deposition of corresponding polyphenols and their metabolites in the brain structures in animals. Therefore, dietary polyphenolics are bioavailable in the brain and can exert protective effect directly in this organ. Although there is no data on phenolic levels in the human brain, one may assume that a diet rich in fruit and vegetables will result in increased cerebral deposition of theses beneficial compounds.

3 Oxidative Stress, Development, and Progression of Cognitive Disorders

3.1 Why Is Brain Susceptible to Oxidative Stress?

All cells, tissues, and organs of human body have a set of enzymes, numerous low-molecular-weight compounds, and metal chelating/sequestrating agents that compose the system of antioxidant defense. In general, the individual links of this system are similar throughout the human body; however, their expression and activity differ between organs. Therefore, under the same conditions of generation of ROS, the capacity of the antioxidant defense in a given organ could be overloaded with free radicals and lead to oxidative damage, but in another one it would not. When two organs have a similar capacity of antioxidant defense but they differ in intensity of generation of ROS, tissues exposed to higher ROS activity will be at a higher risk of peroxidative damage. This situation is complicated by two other factors. Firstly, when a given tissue contains a lot of biomolecules that can rapidly react with ROS with further generation of secondary radicals and cytotoxic products, this will result in a higher cellular destruction. Secondly, tissues can contain high amounts of transition metals (e.g., iron, copper) that are normally "silent" (sequestrated). When these metals are released, they can catalyze conversion of hydrogen peroxide (H_2O_2) into more toxic hydroxyl radicals and induce larger tissue damage. Moreover, high concentration of vitamin C that can maintain oxidation state of these metal cations optimal for hydroxyl radicals generation will augment cell injury (McGrath et al. 2001; Nowak et al. 1991). All these four factors that predispose to peroxidative damage to tissues occur in the brain.

There is a low activity of catalase in the brain. Other key enzymes of antioxidant defense such as superoxide dismutase and glutathione peroxidase reach moderate activities in comparison to those noted in other organs (Lau et al. 2005). Superoxide dismutase catalyzes dismutation of superoxide into oxygen and H_2O_2. H_2O_2 can be subsequently decomposed into water and oxygen by catalase. Glutathione peroxidase uses glutathione as an electron donor and is active with H_2O_2 and also (some isoenzymes) with organic hydroperoxide substrates. Thus, lower activity of these enzymes can increase the possibility of conversion of superoxide and H_2O_2 into highly reactive hydroxyl radicals with subsequent damage to brain biomolecules.

Formation of superoxide radical (and then H_2O_2) in normal tissues is an ongoing process in the respiratory chain electron transport that is localized at the mitochondrial inner membrane.

Electrons given by NADH and succinate pass through the electron transport chain to oxygen which is reduced to water. At a rough estimate, 3–5 % of consumed oxygen undergoes incomplete reduction due to direct leakage of electrons from respiratory chain to oxygen with subsequent formation of superoxide radical. The rate of mitochondrial oxygen consumption determines the rate of superoxide and H_2O_2 formation. The brain constitutes about 2 % of the body mass; however, it utilizes around 20 % of the total oxygen consumption. Thus, the rate of brain mitochondrial oxygen

consumption per g of tissue is very high in comparison to other organs in human body and determines high secondary stream of oxidants capable of damaging brain structures. Additionally, the reaction of oxygen and ROS with brain neurotransmitters can turn on various mechanisms leading to the oxidation of lipids, proteins, and DNA (Pattison et al. 2002).

The brain contains large amounts of lipids including polyunsaturated fatty acids (PUFAs). They are present in neuronal as well as in mitochondrial membranes and are highly susceptible to lipid peroxidation. ROS are the most important initiators of PUFAs peroxidation process that can easily evolve into the propagation phase characterized by excessive formation of fatty and peroxyl-fatty acid radicals with subsequent formation of 4-hydroxy-nonenal and malondialdehyde which in turn are toxic for various cells including neurons (Cheng et al. 2011; Bai and Mei 2011).

Since the brain is not homogeneous in its lipid composition including PUFAs (O'Brien and Sampson 1965), one may assume that some brain regions would be more susceptible to peroxidative attacks. There are relatively high concentrations of iron and ascorbic acid in the brain. Because of the fact that they stimulate lipid and catecholamines oxidation (with subsequent radicals formation) under experimental conditions (Fan et al. 2010; Hašková et al. 2011; Hasegawa et al. 2009), one may assume that they can additionally enhance the risk of ROS-induced damage to brain biomolecules.

Taking into consideration the fact that in the majority of regions of the brain, neuronal cells are post-mitotic and are not able to wash out themselves from accumulated oxidative damage, it can explain the high brain susceptibility to oxidative stress.

3.2 Association Between Persistent Oxidative Stress and Cognitive Dysfunction

Numerous pathogenetic mechanisms leading to the development of neurodegenerative diseases characterized by progressive decline of cognitive performance involve damage to neurons caused by the oxidative stress (Albarracin et al. 2012).

Without the decision whether oxidative stress is the primary or secondary mechanism in the progression of these diseases, one may assume that subjects with a different degree of cognition impairment may present features of systemic or local (in the cerebral tissues) oxidative stress. Therefore, in the last few years, numerous studies comparing biomarkers of oxidative stress in specimens of the brain tissue, cerebrospinal fluid, blood, and urine obtained from subjects with and without cognitive dysfunction or dementia have been executed (Tables 2 and 3).

In general, these studies involved patients with mild cognitive impairment (MCI) that were compared with two additional references group: patients with AD and age-matched controls with normal cognition. The chosen biomarkers reflected intensity of lipid peroxidation (malondialdehyde, hydroxynonenal, F2-isoprostanes), status of low-molecular-weight antioxidants (glutathione, vitamin C), activity of enzymes involved in antioxidant defense (superoxide dismutase, glutathione peroxidase, glutathione

reductase, glutathione-S-transferase) and ROS generation (NADPH oxidase), degree of peroxidative damage to DNA (8-hydroxy-2-deoxyguanosine) and proteins (proteins carbonyls), as well as the iron and cooper metabolism (transferrin saturation, ferritin, iron, and copper concentration).

Patients with mild cognitive impairment (MCI) revealed increased concentration of markers of lipid peroxidation in body fluids (Table 2). They had an increased plasma concentration of malondialdehyde (MDA) (Padurariu et al. 2010; Torres et al. 2011; Umur et al. 2011), as well as the plasma, urinary, and cerebrospinal fluid (CSF) levels of isoprostane 8,12-iso-iPF(2alpha)-VI (Praticò et al. 2002). In addition, in the group of clinically normal subjects, the concentration of F2-isoprostanes in CSF raised over the adult human life span, and the subgroup with biomarker signature of AD (CSF amyloid (A) β(42) and tau) had the highest levels of this biomarker (Montine et al. 2011). Plasma levels of MDA were negatively correlated with cognitive performance expressed with Mini–mental state examination (MMSE) score in MCI patients (Torres et al. 2011). Similar correlation between circulating MDA and MMSE score was observed in the group of elderly residents from nursing homes (Umur et al. 2011).

However, other researches that used F2-isoprostanes to evaluate intensity of lipid peroxidation reported completely opposite results. Plasma and urinary levels of F2-isoprostanes did not discriminate subjects with MCI and AD patients from individuals with no cognitive impairment (Mufson and Leurgans 2010). Moreover, in one prospective study, the concentration of F2-isoprostanes in plasma did not correlate with changes in cognitive function in non-demented older adults over the 8 years of follow-up (Fiocco et al. 2011). Thus, the usefulness of F2-isoprostanes monitoring for prediction of the risk of cognitive decline remains open to question. Perhaps, the measurement of more specific isoprostane 8,12-iso-iPF(2alpha)-VI (Praticò et al. 2002) would give promising results.

Low-molecular-weight antioxidant (total glutathione, GSH, GSH/GSSG ratio) and its metabolite cysteinylglycine were reported to be decreased in plasma of MCI patients (Bermejo et al. 2008; Hernanz et al. 2007).

Both total glutathione and cysteinylglycine positively correlated with total score of cognitive performance in these subjects (Hernanz et al. 2007). Although AD patients presented a low content of GSH in brain tissues as evaluated using noninvasive magnetic resonance spectroscopy, this was not observed in the MCI group (Mandal et al. 2012). Activities of glutathione reductase (involved in the maintenance of high tissue GSH level) and glutathione peroxidase (that uses GSH for tissue protection against oxidants) were suppressed in plasma and erythrocytes of individuals with MCI [(Padurariu et al. 2010; Torres et al. 2011; Umur et al. 2011). These were accompanied by the decrease of serum superoxide dismutase activity (Padurariu et al. 2010). In respect to transition metals predisposing to enhanced peroxidative reactions, patients with cognitive dysfunction had elevated concentration of free iron, ferritin, and transferrin saturation in serum (Umur et al. 2011). Moreover, the increased ratio of copper to iron reflected the increased risk of dementia development in the group of MCI individuals during the 5-year observation (Mueller et al. 2012). Probably, as a result of the decrease in the antioxidant defense and the

Table 2 Results of selected studies on markers of oxidative stress in patients with various impairment of cognitive performance

Studied group	Main results	References
Patients with mild cognitive impairment vs. AD vs. matched controls	Plasma – increased protein carbonyls, decreased GSH, and GSH/GSSG ratio in patients with MCI and AD subjects compared to controls	Bermejo et al. (2008)
Patients with mild cognitive impairment vs. AD vs. matched controls	Plasma – decreased total glutathione and its metabolite cysteinylglycine in AD and MCI patients vs. control. Positive correlations between total score of cognitive performance and glutathione and cysteinylglycine levels in MCI and AD patients	Hernanz et al. (2007)
MCI patients vs. AD patients vs. matched healthy controls	Serum – similarly decreased SOD and GPX activity and increased MDA in MCI and AD patients vs. controls	Padurariu et al. (2010)
MCI patients (mild probable AD) vs. matched healthy controls	Plasma – increased MDA, erythrocytes – decreased glutathione reductase in MCI patients. MMSE score was negatively associated with MDA levels	Torres et al. (2011)
Clinically normal individuals	CSF – significant increase of F2-isoprostanes over the adult human life span. Increased F2-isoprostanes in the subjects with the biomarker signature of AD (CSF amyloid (A) β(42) and tau)	Montine et al. (2011)
Subjects with no cognitive impairment vs. MCI vs. AD	Plasma and urine – F2-isoprostane levels did not differ between these three clinical groups	Mufson and Leurgans (2010)
Subjects with no cognitive impairment vs. MCI vs. AD	GSH content in brain regions using noninvasive magnetic resonance spectroscopy – decreased GSH in AD patients in comparison to controls. MCI did not differ from controls	Mandal et al. (2012)
MCI vs. healthy controls	CSF, urine, plasma – elevated isoprostane 8,12-iso-iPF(2alpha)-VI in MCI patients	Praticò et al. (2002)
Non-demented older adults	No association between plasma F2-isoprostanes and change in cognitive function over 8 years. F2-isoprostanes are not a valuable biomarker in predicting cognitive decline in non-demented older adults	Fiocco et al. (2011)
Amnestic MCI vs. preclinical AD	Brain – postmortem-obtained inferior parietal lobule samples had more protein carbonyls in MCI subjects (despite equal levels of neuropathology)	Aluise et al. (2011)
Non-demented Puerto Rican adults	Urine – higher 8-hydroxy-2-deoxyguanosine concentration was significantly associated with lower global cognitive scores	Gao et al. (2010)
Elderly residents from nursing homes with and without cognitive dysfunction	Serum – increased iron, transferrin saturation, ferritin, and MDA, decreased GPX activity in subjects with cognitive dysfunction. Negative correlation between MMSE score and serum MDA	Umur et al. (2011)
MCI vs. early stage senile dementia vs. subjects with normal cognition	Serum – increase in the ratio of copper to non-heme iron predicted which subjects with MCI would progress to dementia over the 5 years follow-up	Mueller et al. (2012)

AD Alzheimer's disease, *MCI* mild cognitive impairment, *GSH* reduced glutathione, *GSSG* oxidized glutathione, *SOD* superoxide dismutase, *GPX* glutathione peroxidase, *MDA* malondialdehyde, *CSF* cerebrospinal fluid, *MMSE* mini–mental state examination

rise of circulating free transition metals (iron, copper), MCI subjects had increased concentration of protein carbonyls in plasma (Bermejo et al. 2008) and in postmortem-obtained brain specimens (Aluise et al. 2011). Consistently, higher urinary levels of 8-hydroxy-2-deoxyguanosine (marker of DNA oxidation) were associated with lower cognitive performance (e.g., global cognitive score, scores for word list learning, recognition) in a large group of non-demented adults (Gao et al. 2010).

In conclusion, the results mentioned above clearly show that oxidative stress resulting from decreased antioxidant defense and probably from increased deposition of transition metals (Fe, Cu) occurs in subjects with mild cognitive impairment. This oxidant–antioxidant imbalance was strong enough to induce detectable products of peroxidative damage to lipids, proteins, and DNA in circulating blood, cerebrospinal fluid, urine, and brain tissue. Thus, one may assume that oxidative stress may be an important event in the early steps of cognitive disorders.

3.3 Clinical Evidences of Oxidative Stress in Patients with Dementia

Table 3 summarizes results of selected studies on intensity of oxidative stress in patients with dementia and its association with cognitive performance scores. These studies mostly involved AD patients and compared them to matched healthy controls as well as to patients with vascular dementia. AD patients had increased plasma concentrations of both lipid peroxidation products, malondialdehyde and 4-hydroxynonenal (McGrath et al. 2001; Gustaw-Rothenberg et al. 2010), and decreased levels of vitamin C (McGrath et al. 2001). There was a significant increase in 4-hydroxy-2-nonenal bound to transmembrane low-density lipoprotein receptor-related protein1 (LRP1) in samples of hippocampus-obtained postmortem from AD patients (Owen et al. 2010). LRP1 is responsible for the efflux of amyloid-β peptide (the main component of senile plaques in the gray matter of the brain, one of the characteristic features of AD) from the brain to the blood across the blood–brain barrier. Thus oxidative damage to LPR1 can impair transport of amyloid-β peptide with subsequent enhancement of its accumulation in the brain.

In other studies, specimens of brain cortex obtained from AD patients revealed suppression of antioxidant defense (decreased concentration of glutathione and activities of superoxide dismutase, glutathione peroxidase, and glutathione-S-transferase an enzyme detoxifying peroxidized lipids and other xenobiotics) (Ansari and Scheff 2010) and increased activity of NADPH oxidase (Ansari and Scheff 2011) that generates superoxide radicals by transferring electrons from NADPH to O_2. These changes in the brain cortex favoring free radical-mediated processes as well as the plasma levels of 4-hydroxy-2-nonenal were negatively correlated with the scores of cognitive performance (McGrath et al. 2001; Ansari and Scheff 2010, 2011).

Apart from AD patients, decreased circulating total and reduced glutathione was noted in Lewy body dementia and in demented individuals in the course of Parkinson's disease (Gironi et al. 2011). In accordance with the observed

Table 3 Results of selected studies on markers of oxidative stress in patients with dementia

Clinical setting	Main results	References
AD vs. matched healthy controls	Plasma – elevated 4-hydroxy-nonenal, normal MDA, decreased vitamin C. Inversely relation of 4-hydroxy-noneal levels with MMSE score	McGrath et al. (2001)
Vascular dementia patients vs. nonvascular dementia vs. healthy controls	Urine – increased concentration of 8-hydroxyl-deoxyguanosine in vascular dementia patients in comparison to both reference groups	Shi et al. (2012)
Vascular dementia patients vs. AD vs. matched healthy controls	Plasma – increased MDA in both dementia groups vs. controls. Higher MDA in vascular dementia patients than in AD patients	Gustaw-Rothenberg et al. (2010)
AD vs. dementia with Lewy bodies vs. Parkinson's disease with dementia vs. MCI vs. healthy controls	Serum – decreased total and reduced glutathione in groups with dementia	Gironi et al. (2011)
AD (mild/moderate, late stage) vs. MCI patients vs. subjects with no cognitive impairment	Frontal cortex – decreased glutathione, glutathione peroxidase, glutathione-S-transferase, and superoxide dismutase in mitochondrial and synaptosomal fractions of AD patients. Levels of oxidative markers correlated with MMSE scores	Ansari and Scheff (2010)
AD vs. MCI vs. matched healthy controls	Plasma – elevated carbonyl proteins in AD and MCI in comparison to healthy controls	Greilberger et al. (2010)
AD different stages (preclinical, MCI, early, mild to moderate) vs. subjects with no cognitive impairment	Postmortem samples of frontal and temporal cortex – elevated NADPH oxidase activity in AD patients. Negative correlation between NADPH oxidase activity and cognitive performance	Ansari and Scheff (2011)
AD patients vs. age-matched controls	Postmortem samples of hippocampus – significant increase in the levels of the lipid peroxidation product 4-hydroxy-2-nonenal bound to transmembrane LRP1 in AD patients in comparison to controls	Owen et al. (2010)

AD Alzheimer's disease, *MCI* mild cognitive impairment, *MMSE* mini–mental state examination, *MDA* malondialdehyde, *NADPH* nicotinamide adenine dinucleotide phosphate, *LRP1* low-density lipoprotein receptor-related protein1

suppression of antioxidant defense, AD patients had increased concentrations of carbonyl proteins in plasma (Greilberger et al. 2010). However, patients with vascular dementia in comparison to AD subjects revealed higher levels of plasma malondialdehyde (Gustaw-Rothenberg et al. 2010) and increased urinary concentration of 8-hydroxydeoxyguanosine (Shi et al. 2012).

Taking the above into consideration, one may conclude that oxidative stress can occur in different forms of dementia regardless of the specific etiology and pathogenetic mechanism (neurodegenerative disorders, vascular dementia). An overlap between various mechanisms leading to oxidative stress in different forms of dementia and high brain susceptibility to oxidative damage could be the possible explanation of these findings. Moreover, these suggest that pharmacological or dietary interventions that will augment antioxidant defense or suppress ROS generation could be effective in prevention of cognitive disorders.

4 Dietary Plant Polyphenols in Prevention of Cognitive Disorders

4.1 Results of Selected Experiments on Laboratory Animals

In order to find neuroprotective activity of plant polyphenols, several experiments employing animal models of neurodegenerative diseases and dementia have been executed in the last few years. In the majority of them, products rich in plant polyphenols or placebo (added to drinking water or standard chow) were applied to transgenic mice bearing mutations causing AD-like pathology. At the end of treatment, cognitive performance of animals was estimated with battery of various tests (e.g., water maze test, step-down test, step-through test, open field test), and then animals were sacrificed, and samples of brain were subjected to microscopic and molecular analysis.

Tg2576 mice overexpress a mutant form of amyloid precursor protein (APP), and they are a model of early onset familial AD (formation of amyloid plaques in the cerebral cortex and progressive cognitive deficits). Seven-month consumption of wine (Cabernet Sauvignon delivered in drinking water equivalent to 6 % ethanol, about 7 % of the total energy consumption was derived from wine) reduced AD-type neuropathology (lower content of amyloidogenic Aβ1-40 and Aβ1-42 peptides in the neocortex and hippocampus) and attenuated spatial memory decline in comparison to animals drinking 6 % ethanol or water alone (Wang et al. 2006). Since no differences were noted between ethanol and water groups, the authors suggested that phenolics present in this wine (gallic acid, caffeic acid and its derivatives, catechin, gallotannins) can stimulate the nonamyloidogenic processing of amyloid precursor thus preventing formation of Aβ peptides (Wang et al. 2006).

In another study employing the same AD-like pathology, murine model pomegranate juice (rich in ellagic acid, gallic acid, tannins, and anthocyanins) inhibited accumulation of soluble Aβ42 and amyloid deposition in the hippocampus as compared to control mice treated with sugar water (Hartman et al. 2006). Moreover, this 6.5-month dietary supplementation (equivalent to daily polyphenol consumption 0.3–0.6 mg) improved animals' behavior performance including learning ability and visual acuity.

Similarly, 5-month administration of grape seed polyphenolic extract 200 mg/kg/day, delivered in the drinking water, containing mostly catechin and epicatechin monomers and oligomers attenuated AD-type cognitive deterioration and reduced accumulation of soluble high-molecular-weight oligomeric Aβ peptides in the brains of Tg2576 mice (Wang et al. 2008). Moreover, under in vitro conditions, this grape seed extract inhibited oligomerization of synthetic Aβ1-42 and Aβ1-40 peptides (Wang et al. 2008).

Microtubule-associated protein tau is a phosphoprotein that regulates microtubule stability and polymerization. Hyperphosphorylation of tau protein that causes its function disturbance and aggregation with subsequent formation of neuropil threads and neurofibrillary tangles in the brain is observed in numerous neurodegenerative disorders including AD. The same grape seed polyphenolic extract given in the dose of 200 mg/kg/day for 2 months inhibited accumulation of sarkosyl-insoluble tau in the brain of TMHT mice, a model of age-dependent development of tau pathology (Wang et al. 2010). Analysis of pulverized brain tissue lysates with ELISA-based multiplex cell signaling assays showed important suppression of ERK 1/2 kinase activity. Since ERK 1/2 is involved in hyperphosphorylation of tau protein, this may be the mechanism of protective effect of grape seed polyphenols (Wang et al. 2010).

Several experiments were devoted to prove neuroprotective and neuromodulating activity of green tea polyphenols. Catechins are the main bioactive constituents of green tea leaves and account for about 30 % of their dry weight. Catechin, epicatechin, gallocatechin, epigallocatechin, catechin gallate, epicatechin gallate, gallocatechin gallate, and epigallocatechin gallate are included in the green tea extract. Green tea polyphenols protected AD-like mice from decline in learning ability and memory induced by intraperitoneal injection of D-galactose and intracerebroventricular injection of Aβ25-35 peptide (Lü et al. 2006). Restraint stress (6-h inhibition of movement per day with the tube fit closely to the body of the animal for 3 weeks) caused significant cognitive impairment in rats with subsequent decrease of total antioxidant activity and increase of malondialdehyde in brain tissue. Simultaneous addition of green tea extract to feedstuff resulted in the improvement of cognitive performance and normalization of oxidative stress biomarkers (Chen et al. 2009). Green tea polyphenols given in the intragastric dose from 5 to 20 mg/kg for 7 days revealed also antidepressant effect in adult mice (Zhu et al. 2012). Addition of green tea extract to drinking water (final concentration 0.5 %) for 8 weeks significantly improved learning and memory as well as suppressed the acetylcholinesterase activity in cerebrum of older rats (Kaur et al. 2008). This suggests usefulness of green tea polyphenols in prevention of age-related deficits of learning and memory.

Presenilin-1 (PS-1) overexpression is associated with AD by favoring the formation of Aβ peptide with subsequent generation of ROS and amyloid deposition. Feeding normal and apolipoprotein E-deficient mice (ApoE−/−) with the diet without folate and vitamin E and supplemented with iron as a prooxidant resulted in PS-1 overexpression in frontal cortex (Chan and Shea 2006). Addition of apple juice concentrate to drinking water (final concentration 0.5 %) prevented this increase in

both animal groups. Apple derived antioxidants and S-adenosylmethionine present in the juice were believed to be involved in this protection; however, the latter via its effect on normalization of DNA methylation seems to be more important.

Six-month administration of tannic acid (daily dose 30 mg/kg) in PSAPP mice that overproduce human Aβ1-40 and Aβ1-42 peptides decreased formation of amyloid deposits in brain parenchyma in comparison to control animals (Mori et al. 2012). This treatment also reduced the behavioral impairment including hyperactivity, decreased object recognition, and defective spatial reference memory. Molecular analysis of brain parenchyma and supplemental in vitro experiments proved inhibition of β-secretase activity as possible mechanism of protective effect of tannic acid against AD-like pathology (Mori et al. 2012).

SAMP8 mice develop early abnormalities of learning and memory due to overproduction of β-amyloid peptide. Therefore, these animals are a useful model of senescence acceleration and geriatric disorders with increased oxidative stress and neuronal deficit. Addition of oligonol (product of polyphenols oligomerization containing catechin-type monomers and oligomers of proanthocyanidins) to standard diet in the daily dose of 60 mg/kg body weight prolonged life span, improved locomotive activity, and suppressed the inflammatory response in SAMP8 mice infected with mouse hepatitis virus and pinworm (Tomobe et al. 2007).

Taking into consideration the results of abovementioned studies, it seems that plant polyphenols may protect organisms from neurodegenerative diseases and resulting dementia. The mechanisms of this protective action seem more complicated than direct unspecific antioxidant activity (however, this does not exclude the latter) and involve molecular interactions with peptides and reactions leading to amyloid formation and interference with intracellular pathways of signal transduction.

4.2 Epidemiological Data: Results of Cross-Sectional and Longitudinal Studies

Numerous in vitro and in vivo studies on experimental animals proved neuroprotective action of plant polyphenols. This was inspiration for planning and execution of epidemiologic observations on association between dietary ingestion of plant polyphenols/antioxidants, the cognitive performance, and risk of developing neurodegenerative diseases. Table 4 summarizes most important cross-sectional and longitudinal studies on the topics that were published in the last dozen years or so. They involved middle-aged and elderly subjects free of dementia at baseline, and the number of studied groups ranged from around 1,500 to 5,500 subjects, and the duration of follow-up in the case of longitudinal studies ranged from 6 to about 32 years.

Analysis of cross-sectional data obtained from 2031 older subjects revealed association between habitual consumption during the previous year of chocolate, wine, and tea (food products rich in variety of flavonoids) as estimated with validated food frequency questionnaire and performance on battery of 6 cognitive tests. Consumers of chocolate, wine, or tea had significantly higher mean test scores and lower prevalence

Table 4 Cross-sectional studies on relation between dietary intake of antioxidants, vitamins, food products rich in plant polyphenols, and cognitive performance

Aim of the study	Study description	Main results	References
Relation between cognitive tests performance and consumption during the previous year of chocolate, wine, and tea in elderly subjects	Cross-sectional, 2031 subjects (age 70–74 year), 6 cognitive tests, FFQ, multivariate models with adjustments for various sociodemographic variables	Consumers of chocolate, wine, or tea had significantly higher mean test scores and lower prevalence of poor cognitive performance than non-consumers	Nurk et al. (2009)
Relation between cognitive function and dietary intake during the previous year of β-carotene and vitamins C and E in elderly subjects	Cross-sectional, 5,182 subjects (aged 55–95 years), 30-point MMSE, FFQ, multivariate models with adjustments for various clinical and sociodemographic variables	Lower intake of β-carotene was associated with impaired cognitive function. Vitamins C and E intake was without significance	Jama et al. (1996)
Relationship between intake during the previous year of different plant foods and cognitive performance in elderly individuals	Cross-sectional, 2,031 subjects (aged 70–74 years), 6 cognitive tests, FFQ, multivariate models with adjustments for various clinical and sociodemographic variables	Intake of many plant foods (especially carrots, cruciferous vegetables, citrus fruits, high-fiber bread) is associated with better cognitive performance	Nurk et al. (2010)
Association between dietary flavonoid intake and cognitive decline in older persons over 10-year period	Cross-sectional at baseline, longitudinal with 10-year follow-up. 1,640 individuals without dementia (aged ≥65 years), 5 cognitive tests repeated 4 times (including baseline assessment), FFQ at baseline, analyses were adjusted for sociodemographic variables	Higher flavonoid intake was associated with better cognitive performance at baseline. Low flavonoid consumers had higher decline in cognitive performance over 10 years follow-up	Letenneur et al. (2007)
Association between midlife level of total and class-specific polyphenol intake and cognitive performance assessed 13 years later	Longitudinal with 13-year follow-up, 2,574 subjects, six 24-h dietary records for calculation of polyphenol intake at baseline. Four neuropsychological tests performed at the end of study. Analyses were adjusted for sociodemographic variables	High polyphenol intake (including catechins, theaflavins, flavonols, and hydroxybenzoic acids) was associated with better language and verbal memory. Intake of catechins, flavonols, proanthocyanidins was negatively associated with executive functioning	Kesse-Guyot et al. (2012)
Association between the French National Nutrition and Health Program Guideline Score (PNNS-GS) assessed at baseline and cognitive performance evaluated 13 years later	Longitudinal with 13-year follow-up, 2,135 subjects (French cohort) (age at cognitive evaluation 65.5 ±4.6 years) PNNS-GS estimated at baseline, four neuropsychological tests performed at the end of study. Analyses were adjusted for sociodemographic variables	Strong compliance with nutritional recommendations was related to better verbal memory	Kesse-Guyot et al. (2011)

(continued)

Table 4 (continued)

Aim of the study	Study description	Main results	References
Consumption of fruit and vegetable juices (rich in polyphenols) and the risk of incident probable AD in dementia-free Japanese Americans at baseline	Longitudinal with 8-year follow-up, 1,589 subjects. FFQ at baseline. Cognition, dementia, AD criteria evaluated at baseline and at every 2 years. Analyses were adjusted for sociodemographic variables and dietary intake of vitamins C, E, and β-carotene	63 incident cases of probable AD. Significantly lower hazard ratio for probable AD in subjects drank juices at least 3 times per week than in those who drank less often than once per week	Dai et al. (2006)
Does high dietary intake of antioxidants decrease the risk of Parkinson's disease?	Cross-sectional, 5,434 subjects (aged 55–95 years) without dementia, FFQ, all analyses were adjusted for sociodemographic variables	High intake of vitamin E (but not vitamin C, flavonoids, β-carotene) may protect from Parkinson's disease	de Rijk et al. (1997)
Relationship between dietary intake during the previous year of antioxidants (vitamins C and E, flavonoids, β-carotene) and the risk of AD in adults free of dementia at baseline	Longitudinal with 6-year follow-up, 5,395 subjects (aged ≥ 55 years), FFQ, 3-stage protocol for case-finding and diagnosis of dementia and AD performed at baseline, during and at the end of follow-up. All analyses were adjusted for clinical and sociodemographic variables	197 subjects developed dementia (146 had AD); high intake of vitamins C and E was associated with lower risk of AD. Flavonoids and β-carotene protected only in the subgroup of current cigarette smokers	Engelhart et al. (2002)
Association of midlife dietary intake of antioxidants to late-life dementia and its subtypes in dementia-free Japanese Americans at baseline	Longitudinal with 32-year follow-up, 2,459 men (aged 45–68 years) included in the study between 1965 and 1968, 24-h dietary recall and dementia assessment at baseline and several times during the follow-up. Analyses were adjusted for clinical and sociodemographic variables	235 incident cases of dementia (102 AD, 44 vascular dementia). No association between intake of β-carotene, flavonoids, vitamins E and C and the risk of dementia or its subtypes	Laurin et al. (2004)
Relationship between dietary intake during the previous year of antioxidants (vitamins C and E, flavonoids, β-carotene) and the long-term risk of AD in adults free of dementia at baseline	Longitudinal with 10-year follow-up, 5,395 subjects (aged ≥ 55 years), FFQ, 3-stage protocol for case-finding and diagnosis of dementia and AD performed at baseline, during, and at the end of follow-up. All analyses were adjusted for clinical and sociodemographic variables	465 incident cases of dementia (365 AD). Higher intake of vitamin E was associated with lower risk of dementia and AD. Vitamin C, β-carotene, and flavonoids were not protective	Devore et al. (2010)

FFQ food frequency questionnaire, *MMSE* mini–mental state examination, *AD* Alzheimer's disease

of poor cognitive performance than non-consumers. The strongest risk-reducing effect of poor cognitive performance was related to wine then to chocolate consumption (Nurk et al. 2009). Ingestion of tea had a weak effect and significantly reduced the risk of poor cognitive performance only in 2 out of 6 tests. These effects were dose dependent (mean test scores raised with increased intake of this food products); however, a plateau was observed for daily consumption of 75–100 ml of wine, 10 g of chocolate, and 200 ml of tea during the previous year (Nurk et al. 2009).

Two other cross-sectional studies had similar aim and design (Jama et al. 1996; Nurk et al. 2010). They reported association between cognitive function and dietary intake during the previous year of β-carotene and vitamins C and E (Jama et al. 1996) and different plant foods (Nurk et al. 2010) in elderly subjects. Lower dietary intake of β-carotene was associated with impaired cognitive function, while consumption of vitamins C and E was without significance (Jama et al. 1996). On the other hand, subjects with intakes of >10th percentile of fruits, vegetables, grain products, and mushrooms performed significantly better in cognitive tests than those with very low or no intake (Nurk et al. 2010). Combined intake of fruits and vegetables had strongest influence on mean test scores with dose-dependent relation up to daily consumption of 500 g. Analysis of individual plant foods revealed a positive effect of consumption of carrots, cruciferous vegetables, citrus fruits, and high-fiber bread on cognitive performance in elderly subjects (Nurk et al. 2010).

The first 3 longitudinal studies reported in Table 4 were devoted to investigate possible relations between dietary intake of flavonoids (Letenneur et al. 2007; Kesse-Guyot et al. 2012), adherence to rules of good nutrition, and cognitive performance assessed several years later (Kesse-Guyot et al. 2011). Higher dietary ingestion of flavonoids was associated with better cognitive performance in a group of 1,640 older adults free from dementia at baseline (Letenneur et al. 2007). Analysis over the 10-year follow-up revealed higher decline in MMSE score in the subjects with the lowest flavonoid intake (Letenneur et al. 2007).

Similar results were obtained in the study analyzing the effect of total and class-specific polyphenol intake on cognitive performance assessed 13 years later. High total polyphenol intake as well as ingestion of catechins, theaflavins, flavonols, and hydroxybenzoic acids was associated with better language and verbal memory. On the other hand, it should be pointed out that scores on executive functioning were negatively associated with intake of dihydrochalcones, catechins, proanthocyanidins, and flavonols (Kesse-Guyot et al. 2012). The last study from this group analyzed the association between adherence to rules of the French National Nutrition and Health Program and the cognitive performance evaluated 13 years later in the cohort of middle-aged adults (Kesse-Guyot et al. 2011). This program had a set of 9 priority objectives focusing on nutrition and physical activity. Those related to nutrition listed below are: increase fruit and vegetable consumption, reduce dietary fat intake (reduce consumption of saturated fats by 25 %; reduce total fat intake to less than 35 % of total dietary intake), increase consumption of carbohydrates (increase carbohydrate consumption to more than 50 % of total dietary intake through 25 % reduction in simple sugars; 50 % increase in fiber and increased consumption of complex carbohydrates starches), increase consumption of calcium

(reduce vitamin D deficiency by 25 %; reduce by 25 % the number of people with calcium intake below recommended levels), and reduce alcohol intake (reduce calorie intake from alcohol consumption in the general population to no more than two drinks per day). To evaluate the adherence to these rules, the special index score (French National Nutrition and Health Program Guideline Score) was constructed (Estaquio et al. 2008). There was a positive association between this index score and verbal memory and executive functioning (Kesse-Guyot et al. 2011). This suggests that strong compliance with nutritional recommendations in midlife could positively affect cognitive performance in the late life and thus prevent the development of dementia.

Five other studies (one cross-sectional and 4 longitudinal) analyzed the association between dietary intake of antioxidants including consumption of polyphenol-rich vegetable, fruit juices, the risk of neurodegenerative diseases (Parkinson's disease, AD), and the development of late-life dementia (Dai et al. 2006; de Rijk et al. 1997; Engelhart et al. 2002; Laurin et al. 2004). In a studied group of 5,434 subjects without dementia (in which 31 had diagnosed Parkinson's disease), high dietary intake during the previous year of vitamin E estimated with food frequency questionnaire was associated with the lower risk of Parkinson's disease (de Rijk et al. 1997). However, ingestion of other antioxidant plant compounds such us vitamin C, flavonoids, and β-carotene had no protective effect.

One hundred forty-six persons out of the group of 5,395 subjects free of dementia at baseline developed AD during the 6 years of prospective observation. In this group high intake of vitamin C and E was associated with the lower risk of AD; however, consumption of flavonoids and β-carotene had no protective effect (Engelhart et al. 2002). On the other hand, when the subgroup of current cigarette smokers ($n = 1{,}257$) was analyzed separately, the significant protective effect of all compounds was noted (Engelhart et al. 2002). The same group of subjects analyzed again after 10-year follow-up revealed protective effect of higher consumption of vitamin E but not vitamin C, flavonoids, and β-carotene (Devore et al. 2010).

In another study counting 1,589 Japanese Americans observed for 8 years, fruit and vegetable juice consumption at least 3 times per week decreased the risk of AD. Dietary intake of vitamins E, C, and β-carotene as well as tea consumption was not protective (Dai et al. 2006). Similarly, almost 32-year prospective observation of large group of men revealed no association between the midlife dietary intake of vitamins E, C, β-carotene, and flavonoids and the risk of late-life dementia and its subtypes (AD, vascular dementia, combination of AD, and cerebrovascular disease) (Laurin et al. 2004).

Age can induce changes in taste. In older subjects the loss of identification of sour and bitter taste in some regions of the tongue has been described (Nordin et al. 2007). Moreover, the sensitivity to sweetening agents is also decreased (Easterby-Smith et al. 1994; Kennedy et al. 2010). These may influence the food preference and in consequence the dietary intake of flavonoids and other antioxidants in elderly people. Therefore, estimation of dietary intake of plant antioxidants at midlife cannot precisely reflect consumption of these compounds in older people. Similarly, data from food frequency questionnaire (cross-sectional studies) obtained from

elderly subjects can be only partially compatible with their consumption at midlife. Moreover, decline of cognitive performance and dementia can alter dietary habits and subsequently intake of plant polyphenols and other antioxidants. Consequently, it cannot be excluded that lower intake of plant polyphenols and antioxidant vitamins reported in older subjects with worse cognitive performance (cross-sectional studies) was just the secondary effect of these disturbances on food preference.

Nevertheless, all studies except for one (Table 4) in general revealed a positive effect of dietary intake of antioxidant vitamins or plant polyphenols on cognitive performance. Their results need confirmation in further more extensive studies. Since data obtained from food frequency questionnaires have some limitations (especially for the group of elderly subjects), inclusion of monitoring of main phenolic metabolites or total phenolic concentration in plasma or urine in the prospective study protocols could be helpful to overcome interpretation troubles of obtained results.

Another interesting question is that intake of some polyphenols (catechins, flavonols) was simultaneously associated with better language and verbal memory but worse executive functioning (Kesse-Guyot et al. 2012). This suggests at least bidirectional action (beneficial or rather unfavorable) of some plant compounds on cognitive function in humans and requires further studies especially in respect to ingested dose and plasma levels of these compounds.

4.3 Interventional Studies: Results of Randomized, Double-Blind, Placebo-Controlled Clinical Trials

Epidemiologic data on positive association between antioxidant vitamins and plant polyphenols dietary intake and cognitive performance in elderly subjects as well as results of experimental studies on relationship between oxidative stress and cognitive decline inspired scientists to perform interventional studies on effects of diet supplementation with antioxidants and polyphenols on cognitive performance and markers of oxidative stress in humans.

Some promising reports (with randomized, double-blind, placebo-controlled design) on these topics have been published during the last several years (Table 5). Because an increased fruits and vegetables consumption involves increased vitamins, microelements, and numerous polyphenols ingestion, the intervention in the majority of these trials consisted in supplementation with mixture of variety of plant compounds (sometimes not precisely defined chemically) with direct and indirect antioxidant and anti-inflammatory properties.

Part of these studies focused on possible suppression of circulating markers of oxidative stress in AD patients and healthy elderly subjects after oral supplementation with cocktails of plant polyphenols or antioxidant vitamins with or without simultaneous monitoring of cognitive function. Since oxidative stress is involved in the development of AD and subsequent dementia, one may assume that inhibition of oxidative stress may protect from further progression of the disease.

Table 5 Interventional studies (randomized, double-blind, placebo-controlled) on plant polyphenols and antioxidants effect on cognition in various clinical settings

Clinical setting	Intervention	Treatment duration and patients number	Outcome	References
Total plasma homocysteine level in patients with AD	Antioxidant drink, 200 ml/day (polyphenols from apple, lemon, green tea extracts, vitamins B and C)	8 months, 48 patients with AD, 52 controls	Attenuation of the increase in homocysteine level along with time in AD patients	Morillas-Ruiz et al. (2010)
Cognitive performance in healthy elderly women	One capsule (set of antioxidant vitamins, magnesium, selenium) per day	6 months, 220 women (aged 60–91 years)	No effect on cognitive performance in female seniors	Wolters et al. (2005)
Memory function in community -dwelling seniors without dementia	Complex antioxidant blend (34 components, e.g., grape seed extract, ginkgo biloba, gotu kola)	4 months, 86 subjects (aged 50–75 years)	Significant memory improvement	Summers et al. (2010)
Oxidative stress markers in patients with AD	Cholinesterase inhibitor (donepezil 5 mg/day) plus mixture of antioxidants vs. donepezil plus placebo	6 months, 52 patients with AD	Decrease of circulating homocysteine and hydroperoxides	Cornelli (2010)
Cognitive function and circulating isoprostanes and amyloid β in AD patients	Curcumin in a daily dose 0, 1, or 4 g followed by monitoring of curcumin metabolites in plasma	6 months, 34 patients with AD, age ≥ 50 years	No effect on circulating isoprostanes and amyloid β. Inconclusive for cognitive function	Baum et al. (2008)
Cognitive function and circulating lipid peroxidation products in older adults	Flavonoid antioxidant Pycnogenol 150 mg per day (100 mg with breakfast, 50 mg with evening meal)	3 months, 101 healthy adults (age 60–85 years) free of any medications	Significant improvement of spatial working memory. Tendency to decrease circulating F2-isoprostanes	Ryan et al. (2008)

Dementia in Down syndrome subjects over age 40 years	Daily oral antioxidant supplementation (900 IU of α-tocopherol, 200 mg of ascorbic acid and 600 mg of α-lipoic acid)	2 years, 53 individuals with Down syndrome and dementia	Lack of improvement in cognitive performance and inhibition of cognitive decline	Lott et al. (2011)
Memory and cognitive performance in community-dwelling adults without dementia	Vitamins and antioxidants (folic acid, B12, vitamin E, *S*-adenosylmethionine, *N*-acetylcysteine, acetyl-L-carnitine)	3 months, 115 adults (aged 22–73 years)	Significant improvement of memory and cognitive performance	Chan et al. (2010)
Cognitive function in older adults with stable state of health	Dried powdered rosemary in single 458 ml drink of tomato juice (doses 0 mg placebo, 750, 1,500, 3,000, and 6,000 mg)	Cognitive function tested after 1, 2.5, 4, and 6 h after single dose of rosemary (7 day washout between doses), 28 adults (mean age 75 years)	Dose-specific effect on speed memory; at 750 mg significant improvement, at 6,000 mg significant impairment versus placebo	Pengelly et al. (2012)
Memory function in older adults with MCI	Concord grape juice (daily dose 6–9 ml/kg body weight)	12 weeks, 12 adults (78 ± 5 years) with memory decline but not dementia	Significant improvement in verbal learning	Krikorian et al. (2010a)
Memory function in older adults with MCI	Wild blueberry juice (daily dose 6–9 ml/kg body weight)	12 weeks, 16 older adults with memory decline but not dementia	Significant improvement of memory functions	Krikorian et al. (2010b)
Neurocognitive function in older adults with mild age-related memory decline	Concord grape juice (daily dose 6.3–7.8 mL/kg of body weight)	16 weeks, 21 adults (76.9 ± 6.1 years)	Reduced interference during recognition memory	Krikorian et al. (2012)
Neuropsychological functioning of cognitively intact older adults	Cranberry juice (900 g/day of 27 % vol. juice)	6 weeks, 50 community-dwelling adults (age ≥60 years)	No significant effect	Crews et al. (2005)

AD Alzheimer's disease, *MCI* mild cognitive impairment

Concentration of circulating homocysteine that can exert direct neurotoxic effect and induce endothelial dysfunction via promoting oxidative stress is elevated in AD patients. Increased homocysteine levels (even within the normal range) were reported to strongly promote the cognitive decline in AD patients (Oulhaj et al. 2010) and in healthy elderly subjects (McCaddon et al. 2001). Since polyphenols can normalize plasma homocysteine levels in humans, one double-blind placebo-controlled study on the effect of brisk consumption of 200 ml drink rich in antioxidant polyphenols from apple, lemon concentrate juice, apple, green tea extracts, and vitamins B and C on total plasma homocysteine levels in AD patients (initial and moderate phase) has been done (Table 5). Eight-month consumption of this drink significantly attenuated the rise of homocysteine level along with time in AD patients especially in those with moderate phase (Morillas-Ruiz et al. 2010). However, in any studied group (AD patients and age-, sex-, BMI-matched controls), the homocysteine levels after intervention were not lower than at the baseline (Morillas-Ruiz et al. 2010). Therefore, the effect of this treatment was rather weak because it did not decrease (normalized) but only inhibited the rise of total plasma homocysteine levels in AD patients. Since no monitoring of cognitive performance was done, the clinical outcome of this polyphenolic cocktail is not known.

In another placebo-controlled study, 6-month multivitamin supplementation (including 150 mg vitamin C, 36 mg vitamin E, 50 mg magnesium, and 60 μg selenium per day) lowered total plasma homocysteine levels in the group of 220 healthy elderly women without dementia (Wolters et al. 2005). On the other hand, this intervention did not change the cognitive performance in vitamin group comparing to the placebo receivers. Perhaps, the period of lowered homocysteine levels was too short to reveal any positive effect on cognitive performance in this group of healthy women. It should be pointed out that observational studies proving relationship between increased circulating homocysteine and the rate of decline of cognitive performance lasted at least a few years (Oulhaj et al. 2010; McCaddon et al. 2001).

Four-month administration of complex antioxidant blend (34 components including antioxidant vitamins, microelements, ginseng, grape seed extract, gotu kola, ginkgo biloba) reduced circulating homocysteine along with improvement of memory function in community-dwelling seniors without dementia at baseline (Summers et al. 2010).

Mixture of various direct and indirect antioxidants (carnosine, coenzyme Q 10, vitamin E, vitamin C, β-carotene, selenium, L-cysteine, ginkgo biloba, vitamins B1, B2, B3, B6, B9, B12) was also tested in combination with donepezil (cholinesterase inhibitor) in patients with AD. After six-month treatment, significant attenuation of some markers of oxidative stress (hydroperoxides) and circulating homocysteine in comparison to AD patients treated with donepezil plus placebo was noted (Cornelli 2010).

Curcumin (a polyphenolic molecule) is an effective scavenger of reactive oxygen and nitrogen species in vitro and was effective in animal models of AD reducing brain amyloid, plaques, and markers of oxidative stress. However, curcumin given in a maximal oral daily dose of 4 g for 6 months had no significant effect on circulating isoprostanes and serum concentrations of amyloid β (AD biomarker) in patients presenting with progressive decline in memory and cognitive function for half of the

year (probable or possible AD) (Baum et al. 2008). Although MMSE scores were noted for all participants at baseline and at the end of treatment, the study was inconclusive for any effect of curcumin on cognitive performance since there was no decline in cognitive function in the group treated with placebo over the study period (Baum et al. 2008). Pycnogenol (the trade name for a specific blend of procyanidins extracted from the bark of French maritime pine with strong antioxidant properties, Horphag Research, Geneva, Switzerland) given in the daily oral dose 150 mg for 3 months significantly improved spatial working memory while had no distinct effect on plasma concentration of lipid peroxidation products in healthy older adults (Ryan et al. 2008).

Effect of fruit juice consumption (Concord grape juice, wild blueberry juice, cranberry juice) on cognitive function in older subjects with and without MCI is the main feature in the second group of these interventional studies (Table 5). Moreover, this group involves also trials with dried rosemary leaf powder and combination of vitamins with antioxidants on neurocognitive performance in older adults and subjects with Down syndrome and dementia (Lott et al. 2011; Chan et al. 2010; Pengelly et al. 2012). Consumption of Concord grape juice or wild blueberry juice in a daily dose 6–9 ml/kg body weight for 12 weeks revealed some neurocognitive effects in older subjects with early memory decline but not dementia (Krikorian et al. 2010b). This consisted of significant improvement in a measure of verbal learning and nonsignificant enhancement of verbal and spatial recall (Krikorian et al. 2010a). Results of this study were confirmed recently with the same daily dose of Concord grape juice consumed for 16 weeks. Active treatment group revealed reduced interference during recognition memory versus placebo group (Krikorian et al. 2012). Moreover, functional magnetic resonance imaging revealed increased activity in the right anterior and posterior regions of the brain cortex during performance of memory tasks after supplementation with the concord grape juice (Krikorian et al. 2012), which may suggest greater hemodynamic response and neuronal activity. On the other hand, cranberry juice consumed for 6 weeks had no significant effect on neuropsychological functioning (assessed by a battery of tests, e.g., selective reminding test, Wechsler Memory Scale III Faces I and Faces II subtests) of community-dwelling, cognitively intact older adults (Crews et al. 2005). Similar results were found in individuals with Down syndrome and dementia. Although 2 years supplementation with antioxidants (α-tocopherol, ascorbic acid, and α-lipoic acid) was safe, well tolerated, and increased about 2 times the plasma levels of α-tocopherol in these subjects, no improvement in cognitive performance and inhibition of cognitive decline was noted compared to the placebo group (Lott et al. 2011).

In another study composition of vitamins and antioxidants (folic acid, B12, Vitamin E, *S*-adenosylmethionine, *N*-acetylcysteine, and acetyl-L-carnitine) improved memory and cognitive performance in adults without dementia (Chan et al. 2010). However, performance declined to baseline following withdrawal of this treatment (3 month washout) and again statistically improved when subjects involved in the study resumed taking this supplementation for three additional months (Chan et al. 2010).

The study on short-term effect of various single doses of dried rosemary leaf powder (R. officinalis L. from 750 mg to 6,000 mg) on cognitive performance

revealed a very interesting dose-dependent effect (Pengelly et al. 2012). Lower doses (750 mg, almost equal to normal culinary consumption) improved the speed memory in older adults. The highest dose of 6,000 mg had opposite effect – significantly impaired the speed memory as estimated with Cognitive Drug Research computerized system at 1 to 6 h of post-ingestion. Similarly, biphasic dose–response curve was noted for self-reported alertness with computerized questionnaire scale (Bond–Lader Visual Analogue Scales of Mood and Alertness) (Pengelly et al. 2012).

Although the majority of these trials revealed positive effects of dietary interventions on circulating markers of oxidative stress and cognitive performance, they should be recognized as pilot studies that can be used for future planning of more extensive trials. As one can see from Table 5, these studies have some limitations. Low number of studied patients/volunteers and relatively short duration of dietary supplementation seem to be the most important factors suggesting caution for application of these results into clinical practice. The majority of these studies (9 of 13) involved older adults in a stable state of the health with or without mild impairment of cognitive performance. For that reason, their results could be rather applicable for prevention than for treatment of cognitive disorders.

Dietary supplementation included consumption of various juices, combination of direct and indirect antioxidants (vitamins, plant phenolics, microelements), plant extracts, and just dried leaves. Thus, in some cases the observed improvement of cognitive performance or suppression of circulating markers of oxidative stress could be the result of simultaneous action of several dozen of bioactive compounds including polyphenols. In addition, dietary polyphenols before absorption into the blood could be transformed into less complex compounds by gut microflora (Aura 2008). Therefore, the composition of polyphenols supplement may differ significantly from that absorbed and reaching brain tissues with circulating blood. Taking these into consideration, it is necessary to determine active substance or substances responsible for improvement of cognitive performance in order to construct the most effective supplement. It is interesting to investigate whether supplementation-induced improvement of cognitive performance is stable or transient. What dose of polyphenols is necessary for the maintenance of the positive effect? Only one study of those listed in Table 5 tried to answer these questions. In this study improved memory and cognitive performance after 3-month supplementation with vitamins and antioxidants declined to baseline already after 3-month washout period. Moreover, they raised again significantly after consecutive 3-month supplementation (Chan et al. 2010). This indicates that the effect of supplementation is reversible, and its maintenance needs continuous addition of these antioxidants into the diet.

Another question is the optimal daily dose of dietary supplements that can improve or inhibit decline in cognitive performance in elderly subjects. As was shown in the study with short-term effect of rosemary on speed memory, the supplement can improve or damage cognitive performance depending on the amount of ingested active substance. These questions should be solved in future trials. To do this, more extensive studies with a large number of patients with different stages of cognitive impairment, various doses of supplements, and longer duration of dietary intervention are necessary.

5 Future Directions

Some important questions necessary to solve were already listed at the end of the last subchapter. However, having established set of plant polyphenols (or their metabolites) with anti-neurodegenerative activity, we should ask the following questions: is it necessary to use them for dietary supplementation? What about addition to the diet of food products with high content of these compounds?

Polyphenols are almost ubiquitous in plant foods. Therefore, it seems that their content in the average diet would be sufficient to cause neuroprotection and inhibit age-related cognitive decline under condition of better absorption from the gastrointestinal tract into the blood. Dietary polyphenols are poorly absorbed in the small intestine, and the majority of them can reach the colon where they are exposed to action of variety of enzymes synthesized by the colon microbiota. These enzymes can hydrolyze glycosides, glucuronides, sulfates, amides, esters, and lactones. Apart from reactions of reduction, decarboxylation, demethylation, and dehydroxylation, they can also break down the polyphenolic backbone structure, thus producing numerous efficiently absorbed low-molecular-weight metabolites. Therefore, it seems that stimulation of intestinal growth of bacterial species that effectively process dietary polyphenols into easily absorbed compounds with neuroprotective activity would be another approach. This could be obtained with the usage of appropriate probiotics and/or prebiotics and would not require additional dietary supplementation with plant polyphenols.

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