Neurotox Res (2016) 30:345–366
DOI 10.1007/s12640-015-9590-4

ORIGINAL ARTICLE

Are Polyphenols Strong Dietary Agents Against Neurotoxicity and Neurodegeneration?

Susana Almeida[1] · Marco G. Alves[2] · Mário Sousa[1,3] · Pedro F. Oliveira[1,4] · Branca M. Silva[2]

Received: 17 July 2015 / Revised: 10 December 2015 / Accepted: 12 December 2015 / Published online: 8 January 2016

Abstract Life expectancy of most human populations has greatly increased as a result of factors including better hygiene, medical practice, and nutrition. Unfortunately, as humans age, they become more prone to suffer from neurodegenerative diseases and neurotoxicity. Polyphenols can be cheaply and easily obtained as part of a healthy diet. They present a wide range of biological activities, many of which have relevance for human health. Compelling evidence has shown that dietary phytochemicals, particularly polyphenols, have properties that may suppress neuroinflammation and prevent toxic and degenerative effects in the brain. The mechanisms by which polyphenols exert their action are not fully understood, but it is clear that they have a direct effect through their antioxidant activities. They have also been shown to modulate intracellular signaling cascades, including the PI3K–Akt, MAPK, Nrf2, and MEK pathways. Polyphenols also interact with a range of neurotransmitters, illustrating that these compounds can promote their health benefits in the brain through a direct, indirect, or complex action. We discuss whether polyphenols obtained from diet or food supplements are an effective strategy to prevent or treat neurodegeneration. We also discuss the safety, mechanisms of action, and the current and future relevance of polyphenols in clinical treatment of neurodegenerative diseases. As populations age, it is important to discuss the dietary strategies to avoid or counteract the effects of incurable neurodegenerative disorders, which already represent an enormous financial and emotional burden for health care systems, patients, and their families.

Keywords Polyphenols · Antioxidants · Catechins · Neurodegeneration · Brain · Neurotoxicity · Signaling pathways

Introduction

Dietary polyphenols exhibit a strong potential to counteract neurotoxicity and neurodegeneration. In recent years, evidence has been produced suggesting that dietary polyphenols can prevent the development of serious complications associated with neurodegenerative disorders, as well as take part in a therapeutic strategy to attenuate the deleterious effects promoted by those same disorders. The pathophysiology of neurological disorders is complex and few clinically relevant medicines are available in the market to combat Alzheimer's disease (AD), stroke, multiple sclerosis (MS), Parkinson's disease (PD), Huntington's disease (HD), or other neurodegenerative diseases. The few available options are expensive and have limited efficacy. For example, interferon β-1a is used for MS (Lampl et al. 2012); levodopa is used for PD (Singer 2012);

Susana Almeida and Marco G. Alves have contributed equally to this work.

✉ Branca M. Silva
bmcms@ubi.pt

[1] Department of Microscopy, Laboratory of Cell Biology and Unit for Multidisciplinary Research in Biomedicine (UMIB), Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal

[2] CICS-UBI, Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal

[3] Centre for Reproductive Genetics Prof. Alberto Barros, Porto, Portugal

[4] I3S - Institute of Health Research and Innovation, University of Porto, Porto, Portugal

tetrabenazide is used for HD (de Tommaso et al. 2011), and tissue type plasminogen activator (tPA) is available for stroke (Haile et al. 2012). The high cost and limited efficacy of these treatments emphasizes a clear demand for alternative therapies. In this context, dietary polyphenols have emerged as a possible source of bioactive molecules with the capacity to exert a positive action against neurotoxicity and neurological diseases. The etiology of neurological disorders is very complex but most of those diseases present common features, including mitochondrial dysfunction, oxidative stress, genetic alterations, regulation of cytokines expression, inflammation and modification of signaling pathways. In fact, polyphenols are reported to alter signaling pathways and induce cell death through both apoptosis and autophagy, an evolutionarily conserved mechanism of lysosomal proteolysis in eukaryotes, which occurs in response to nutrient deprivation. This property of polyphenols to trigger autophagy is important in the treatment and prevention of neurodegenerative diseases, since decreased autophagic degradation and mitochondrial protein aggregates are particularly harmful in post-mitotic cells (such as neurons), whose loss is observed in these disorders (Pallauf and Rimbach 2013).

Polyphenols are found in a variety of alimentary sources, including beverages, (such as tea and red wine), herbs, seeds, fruits (such as apples, berries, and cocoa), and also in extra virgin olive oil (EVOO) (for extensive review (Perez-Jimenez et al. 2010; Rigacci and Stefani 2015)). Flavonoids are among the most abundant polyphenols in human diets, representing about 2/3 of all those ones ingested. Phenolic compounds incorporate in their structure one or more benzenic rings with one or more hydroxyl groups. Most polyphenols are synthesized by the phenylpropanoid metabolic pathway (shikimate pathway), in which phenylalanine is used to produce 4-coumaroyl-CoA. In flavonoids biosynthesis, 4-coumaroyl-CoA incorporates three units of malonyl-CoA (acetate pathway), forming a polyketide before differentiating into chalcones, which are precursors for all of the flavonoid structures. The metabolic pathway continues through a series of modifications to yield flavanones, then dihydroflavonols and latter anthocyanins. Along this pathway, many other classes of flavonoids can be formed, namely flavonols, flavan-3-ols (catechins), and proanthocyanidins (tannins) classes. The flavonoids, which encompass a large number of secondary metabolites, present a structure of two benzenic rings (A and B) and a three-carbon bridge that can usually form a third ring (C) (Dewick 2002).

There are numerous polyphenols and their bioactivity depends on their structure, concentration, and availability at the site of action. Indeed, to have any relevance in neurotoxicity and neurodegeneration, dietary polyphenols must cross the blood–brain barrier (BBB). As will be discussed in the next subchapters, several of these compounds have already proven capacity to cross the BBB and exert their action in the brain (Faria et al. 2010). Moreover, there is an enormous geographical variability on the human intake of polyphenols. Thus, it is very difficult to evaluate the contribution of each source to the overall effect of polyphenols. Here, we present an up-to-date overview of the possible therapeutic potential of dietary polyphenols against neurotoxicity and neurodegeneration. We will discuss the question: are polyphenols dietary agents against neurotoxicity and neurodegeneration? In this discussion, we stress that while exciting new discoveries have been made, which make this subject important to discuss, a definitive conclusion is far from being reached. We propose to discuss diet as a natural source of phytochemicals with potential to protect the brain from neurodegeneration. Among those phytocompounds, we focused on polyphenols, particularly catechins.

Edible and Medicinal Plants as a Source of Polyphenols

Plants have played an important role in modern civilization. They serve not only as a natural source of compounds with therapeutic potential but also as an alternative source of drugs. According to the World Health Organization, a medicinal plant is any plant that contains substances that are of interest for therapeutic purposes, or that contains precursors for chemo-pharmaceutical semisynthesis. Medicinal plants can have any or all of its morphological parts including leaves, roots, rhizomes, stems, barks, flowers, fruits, grains or seeds, employed in the control or treatment of a particular disease or group of medical conditions. These non-nutrient plant chemical compounds are referred as phytochemicals (from the Greek *phyto* meaning 'plant') (Doughari 2012). In a more complex and detailed definition, we can describe phytochemicals as structurally diverse secondary metabolites, synthesized not only by plants but also by non-pathogenic endophytic microorganisms living within plants. Notably, these metabolites are essential to plants since they help them to survive under environmental stresses, protect them from microbial infections and environmental pollutants, provide them a defense from herbivorous organisms, and attract natural predators of such organisms, as well as lure pollinators and other symbiotes (Leonov et al. 2015; Stefani and Rigacci 2014; Wink 2003).

Polyphenols are one of the largest groups of phytochemicals with important roles in plants, including protection from photosynthetic stress and reactive oxygen species (ROS). For instance, they help plants to survive various environmental stresses, including UV light, heat

and cold stresses, osmotic stress and high salinity, extreme pH, water deficit, dehydration, and even nutrient deprivation. They protect plants from viral, bacterial, yeast and fungal infections, defend plants from invading insects, herbivorous animals and competitor plant species. There is also evidence supporting that these phytochemicals are beneficial to survival and reproduction of plants (Leonov et al. 2015). Indeed, the synthesis of polyphenols (and many other phytochemicals) in plants is induced by a wide range of environmental stresses. Notably, it has been shown that polyphenolic profile provides a chemical signature of the environment state. For instance, the xenohormesis hypothesis postulates that plants synthesize phytochemicals as part of a response to hormetic environmental stresses, such as UV light, thermic stresses, osmotic stress and high salinity, water deficit and dehydration, nutrient deprivation, and infection (Howitz and Sinclair 2008; Lamming et al. 2004). As referred, there is an enormous variability on the intake of polyphenols by individuals from different countries. Still, more than 1 g of phytochemicals *per* day is commonly ingested in diet (Ovaskainen et al. 2008; Si and Liu 2014). Moreover, as dietary flavonoids are known to occur in lower amounts than the simpler phenolic acids, several studies have shown these latter ones are consumed in greater quantity than flavonoids (Ovaskainen et al. 2008; Perez-Jimenez et al. 2010). It is estimated that individual flavonoid consumption is approximately 190, 313, and 454 mg *per* day, respectively, for the citizens of the United States, Spain, and Australia (Chun et al. 2007; Johannot and Somerset 2006; Zamora-Ros et al. 2010). These substances are biologically active and known to provide health benefits for humans (Hasler and Blumberg 1999).

There are more than 4000 phytochemicals cataloged. Of these, only a small fraction of about 150 phytochemicals have been studied in detail, and several functions were already attributed to these compounds. For example, they stimulate mechanisms that protect the human body from infections, they also counterbalance free radicals, and suppress enzymes that produce carcinogens and activate enzymes that degrade carcinogens. Phytochemicals are described as having protective effects against complex diseases such as diabetes mellitus, high blood pressure, and macular degeneration (Richa Tyagi et al. 2015). Notably, they are suggested to be obligatory in a healthy diet. They are also reported to slow aging and counteract problems arising from health problems including heart sickness, cancer, cataracts, stroke, high blood compression, osteoporosis, and urinary tract infections (Richa Tyagi et al. 2015) (For review see (Boeing et al. 2012)).

Phytochemicals are structurally diverse chemical compounds. Based on their chemical nature they can be divided into the following major classes: (1) phenolic compounds (including flavonoids, phenolic acids, namely hydroxybenzoic and hydroxycinnamic acids, lignans, tyrosol esters, stilbenoids, and alkylresorcinols); (2) terpenes (including monoterpenes and sequiterpenes, sterols, triterpenes and saponins, and carotenoids); (3) betalains (including betacyanins and betaxanthins); (4) organosulfur compounds; (5) organic acids; (6) quinones; (7) methylxanthines; and (8) alkaloids (Hansen and Halkier 2005; Hooper et al. 2010; Kennedy and Wightman 2011; Leonov et al. 2015; Menendez et al. 2013; Si and Liu 2014; Somani et al. 2015; Wu et al. 2014) (Fig. 1). Phenolic compounds are one of the largest and most studied groups of phytochemicals.

As discussed in the previous section, dietary polyphenols are phytochemicals with very interesting properties. They are categorized according to the nature of their carbon skeleton, ranging from basic phenolic molecules to the highly complex flavonoids, the most common and widely studied of all classes of phenolic compounds (Roche et al. 2015; Scalbert et al. 2005). The phenolic compounds, in general, and the flavonoids, in particular, represent an important component of a normal human diet (Kennedy and Wightman 2011). Flavonoids are categorized into flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids (Hollman and Katan 1999), being that catechins remain as one of the groups with the most powerful bioactivity and medicinal relevance. Indeed, catechins (also known as flavan-3-ols or simply flavanols) and their derivatives are the main class of phenolic compounds present in several plants (Fig. 2). Some of the major catechins are (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epigallocatechin 3-gallate (EGCG) (Dias et al. 2013, 2014; Moderno et al. 2009; Nunes et al. 2014). EGCG is the most abundant catechin in tea (*Camellia sinensis* L.) leaves and has been extensively studied (Fresco et al. 2006; Nunes et al. 2014; Seeram et al. 2006; Wheeler and Wheeler 2004; Yang et al. 2004). The health benefits attributed to catechins are suggested to be due to their chemical structure. Catechins are composed of two aromatic rings (A and B) linked by a dihydropyran heterocyclic ring (C) and are characterized by the presence of several hydroxyl groups, in different positions in the general chemical structure (Braicu et al. 2013; Nunes et al. 2014) (Fig. 3). Their structural differences rely mainly on the presence and number of different groups attached to the aromatic rings (Braicu et al. 2013; Dias et al. 2014; Moderno et al. 2009). EC has two hydroxyl groups in the A ring (at carbons 5 and 7), an ortho-dihydroxil group in the B ring (at carbons 3′ and 4′) and one hydroxyl group in the C ring (at carbon 3). EGC and ECG are similar to EC, but EGC has a trihydroxyl group at carbons 3′, 4′, and 5′ on the B ring (instead of an ortho-dihydroxil group), while ECG has a gallate moiety esterified at carbon 3 of the C ring (instead of a

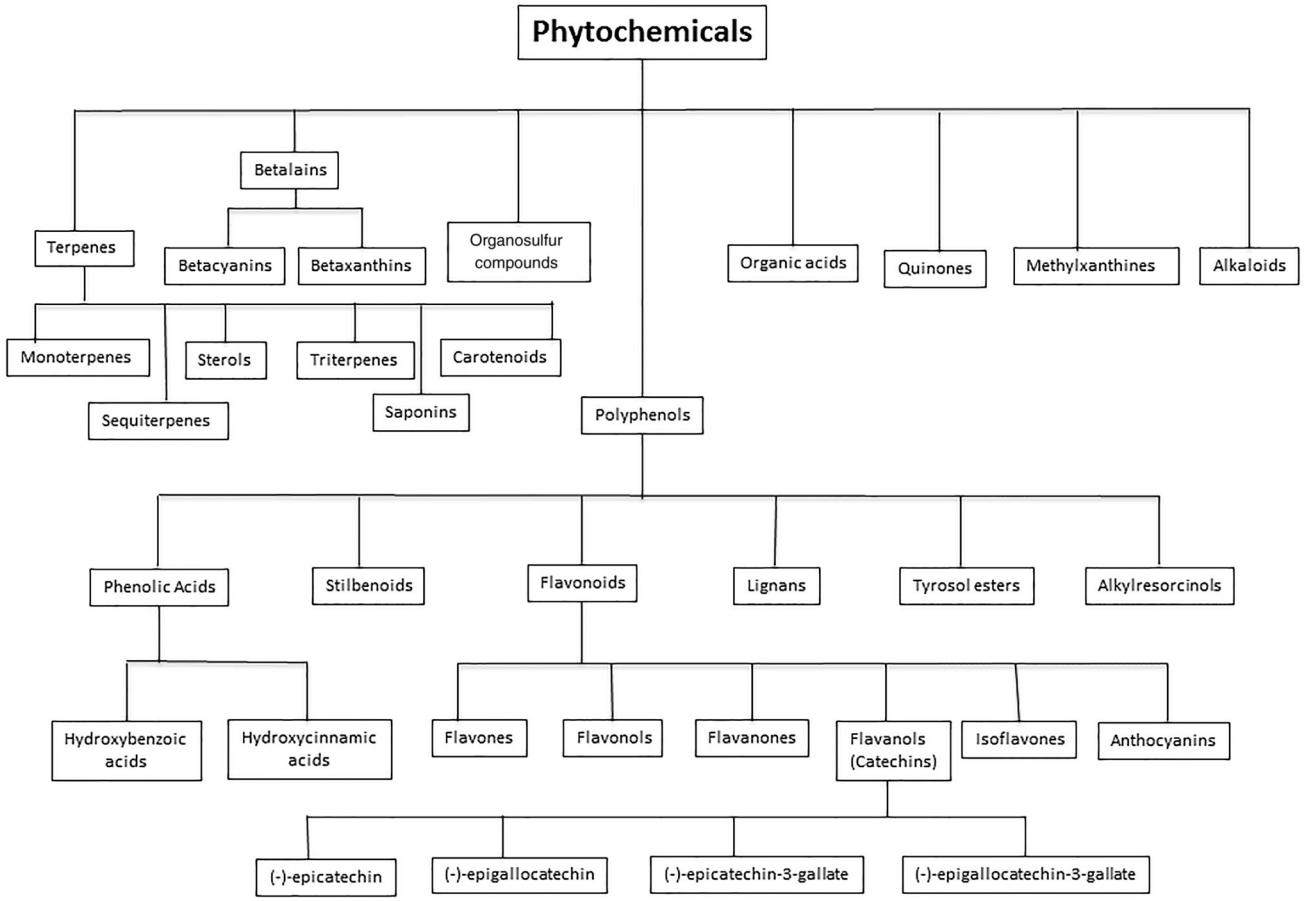


Fig. 1 Schematic drawing of the major classes of phytochemicals. There are eight major classes: phenolic compounds, terpenes, betalains, organosulfur compounds, organic acids, quinones, methylxanthines, and alkaloids. From all classes, polyphenols are one of the largest groups of phytochemicals and one of the most studied

hydroxil group). EGCG has both a trihydroxyl group at carbons 3′, 4′, and 5′ on the B ring and a gallate moiety esterified at carbon 3 on the C ring (McKay and Blumberg 2002; Nunes et al. 2014). Unfermented teas, such as white and green tea, are well-known for their high contents of these compounds. It has been proposed that the galloyl moiety is responsible for the main specific activities of tea catechins, especially lipid lowering effect (Braicu et al. 2013; McKay and Blumberg 2002). Furthermore, the two catechins with galloyl moiety (EGCG and ECG) are reported to possess the most potent biological activities (Kim et al. 2014a). The most abundant green and white teas polyphenol, EGCG, have been suggested to be responsible for most of the beneficial effects of these beverages in clinical and animal studies as well as in the in vitro studies (Basu et al. 2010; Chyu et al. 2004; Dias et al. 2013; Kim 2008; Kim et al. 2007; Nunes et al. 2014; Potenza et al. 2007; Shanafelt et al. 2009). The most described mechanism for the beneficial health effects of EGCG is attributed to its antioxidant properties (Chen and Zhang 2003). Nevertheless, recent findings suggest that autophagy should also be taken into consideration when discussing EGCG action (Kim et al. 2013). However, the mechanisms of action of these compounds are very variable and remain a matter of intense research.

Neurodegeneration at a Glance

Etymologically, the word "neurodegeneration" is composed of the prefix "neuro-," which designates nerve cells, and suffix "degeneration," which in the case of tissues or organs refers to a process of losing structure or function. Thus, in the strict sense, neurodegeneration corresponds to any pathological condition primarily affecting neurons which induces loss of their structure or function. Neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological properties that result in neuronal anatomic or functional malfunctioning. Most of these diseases are reported as arising for unknown causes and progress in a relentless manner. There are hundreds of neurodegenerative disorders, from which we

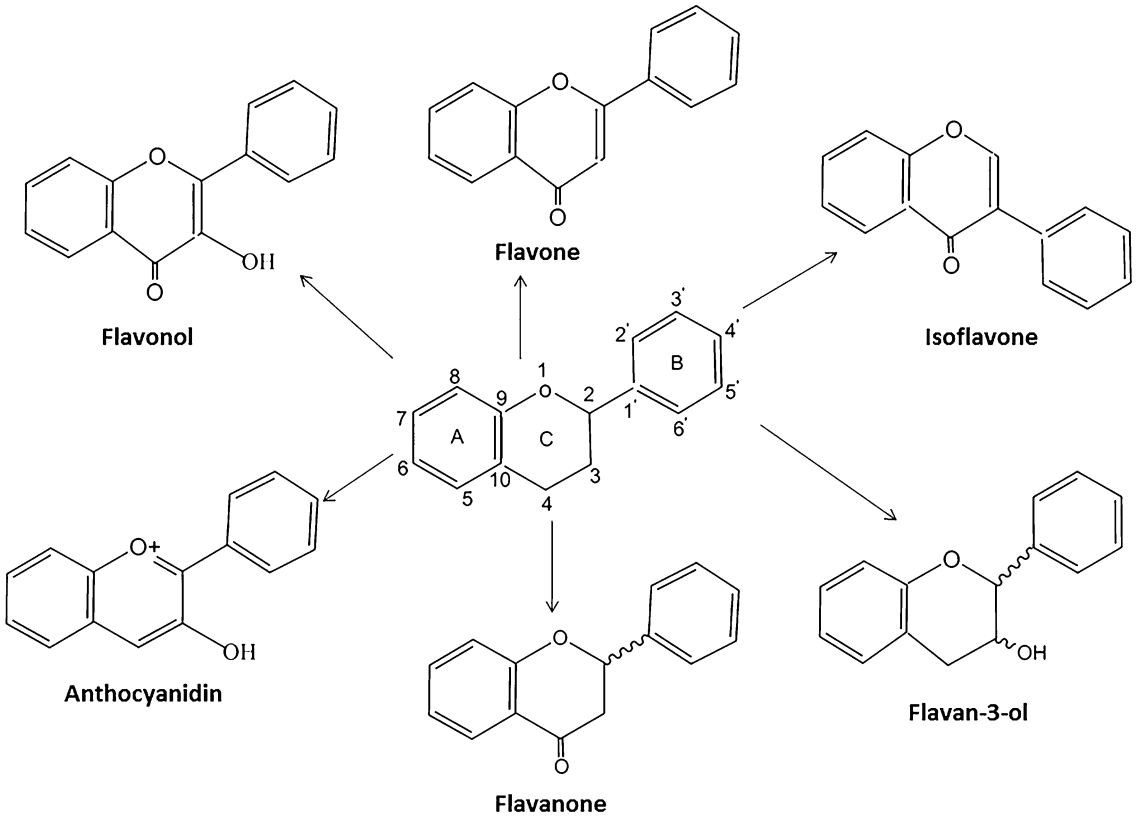
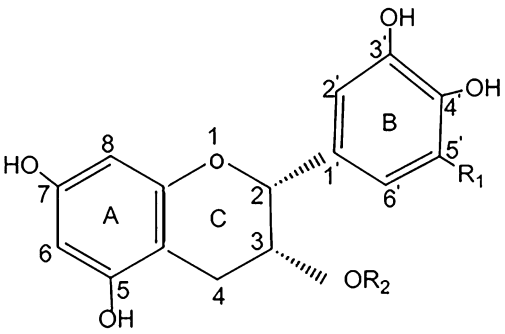


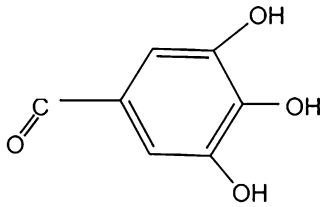
Fig. 2 General structure of a flavonoid (and its numeration system) and chemical structures of the main classes of flavonoids. The basic flavonoid structure is the flavan nucleus, consisting of two aromatic rings (*A* and *B*) linked by a three-carbon aliphatic chain, which normally has been condensed to form a pyran ring. This large group of polyphenols can be classified into several classes according to the oxidation and pattern of substitution of their central *C* ring

highlight a small group that includes AD, PD, HD, and amyotrophic lateral sclerosis (ALS) (Przedborski et al. 2003). It has been consistently reported that the most reliable risk factor for developing a neurodegenerative disorder, especially AD or PD, is aging (Van Den Eeden et al. 2003). Although these diseases have different clinical features, the causal mechanisms at the cellular level appear to be similar. The majority of neurodegenerative diseases are defined as complex multifactorial disorders, as both familial and sporadic forms are known, with genetic and environmental factors contributing to its onset. AD, PD, and ALS are the three major neurodegenerative diseases. AD and PD are the most studied due to their severity and large occurrence in aged populations. Protein misfolding is a complex and multistep phenomenon eventually leading to amyloid formation that is the basis of a variety of diseases, including AD and PD. AD is characterized by cognitive decline and is etiologically related to amyloid deposition (Ho et al. 2005). Notably, this cognitive decline was reported as significantly reduced through the consumption of green tea (Kuriyama et al. 2006). Neurodegenerative diseases represent an increasing social and economic burden to our aging societies. Some reports suggest that 15 % of population over 65 years suffer from AD and 1 % from PD (Cantuti-Castelvetri et al. 2000). The United Nations have reported that the number of people suffering from age-related neurodegeneration, particularly from AD, will exponentially increase from 25.5 million in 2000 to an estimated 114 million in 2050 (Jellinger 2006; Wimo et al. 2003). Neurodegeneration shortens the life expectancy of affected patients, but not all neurodegenerative disorders are fatal per se, and some of the deleterious effects can be counteracted (Przedborski et al. 2003). The brain and nervous system are very prone to oxidative stress (OS) since they are inadequately equipped with antioxidant defenses. Indeed, increased oxidative damage, mitochondrial dysfunction, accumulation of oxidized aggregated proteins, inflammation, and defects in protein clearance are key events that lead to pathologies by targeting neurons (Halliwell 2006). Besides neurons, all of the central nervous system (CNS) is sensitive to OS and suggested to be the basis of neurodegenerative diseases development (Nunes et al. 2014; Valko et al. 2007). Thus, there is compelling evidence that OS plays a critical role in the establishment of neurodegenerative



Main catechin structure

	R1	R2
(-) - Epicatechin	H	H
(-) - Epigallocatechin	OH	H
(-) – Epicatechin-3-gallate	H	Gallate group
(-) – Epigallocatechin-3-gallate	OH	Gallate group



Gallate group

Fig. 3 Chemical structures of the main tea catechins. Figure illustrates two aromatic rings (*A*, *B*) and a dihydropyran heterocyclic ring (*C*), which is the basic structure of flavonoids. The (−)-epicatechin (EC) is constituted by an ortho-di-hydroxil group in the B ring (at carbons 3′ and 4′) and a hydroxyl group in the *C* ring (at carbon 3), and its ester derivative (−)-epicatechin 3-gallate (ECG) differs in this structure by possessing an additional gallate moiety esterified in the *C* ring, at carbon 3. On the other hand, (−)-epigallocatechin (EGC) contains a trihydroxil group on the B ring (at carbons 3′, 4′ and 5′) and its ester derivative (−)-epigallocatechin 3-gallate (EGCG) additionally possesses an esterified gallate at the carbon 3 of the *C* ring

diseases by inducing neuronal loss and neurodegeneration (Ischiropoulos and Beckman 2003).

Only a very low percentage of neurodegenerative diseases are caused by genetic mutations. Indeed, the largest percentage is suggested to be caused by OS and other deleterious effects, including mitochondrial dysfunction, that lead to the formation of neurotoxic molecules. Among the several mechanisms proposed to occur, evidence shows that promotion of apoptosis or programmed cell death is a key event (Winner et al. 2011). As discussed, aging is the greatest risk factor for neurodegenerative diseases. Curiously, OS and mitochondrial DNA mutations are also associated with aging (Lin and Beal 2006), although consensus has not been reached as to whether they are cause or consequence. Toxic environmental factors may also initiate neurodegenerative processes. There are reports showing that some neurodegenerative conditions arise in geographic or temporal clusters. A clear example is the case for the PD–ALS complex, which has been suggested to be due to a toxic compound present in *Cycas circinalis* L., an indigenous plant commonly ingested as a food or medicine by indigenous Chamorro people of Guam and other Mariana islands in the Western Pacific (Kurland 1988; Przedborski et al. 2003). Indeed, environmental factors can cause metabolic changes in humans that either increase the production of reactive oxygen and nitrogen species (ROS and RNS) or decrease the antioxidant action associated with increased lipid peroxidation, protein, and DNA oxidation (Aseervatham et al. 2013; Mylonas and Kouretas 1999). Oxidized proteins accumulate in cells via aggregations causing mitochondrial damage, which in turn causes protein damage (Giordano et al. 2014). ROS also damages DNA, leading to aberrant cell cycle, and further deregulation of several crucial growth factors, including *p53* and *Wnt,* that are key players in neurodegenerative diseases and cancer (Driver 2014). Therefore, several factors besides aging, such as environmental factors, are implicated as the basis of neurodegeneration (Fig. 4). As mentioned, dietary polyphenols have important antioxidant properties and are probably the most studied phytochemicals. As a consequence, they are rapidly gaining attention as promising candidates for clinical testing toward the protection against

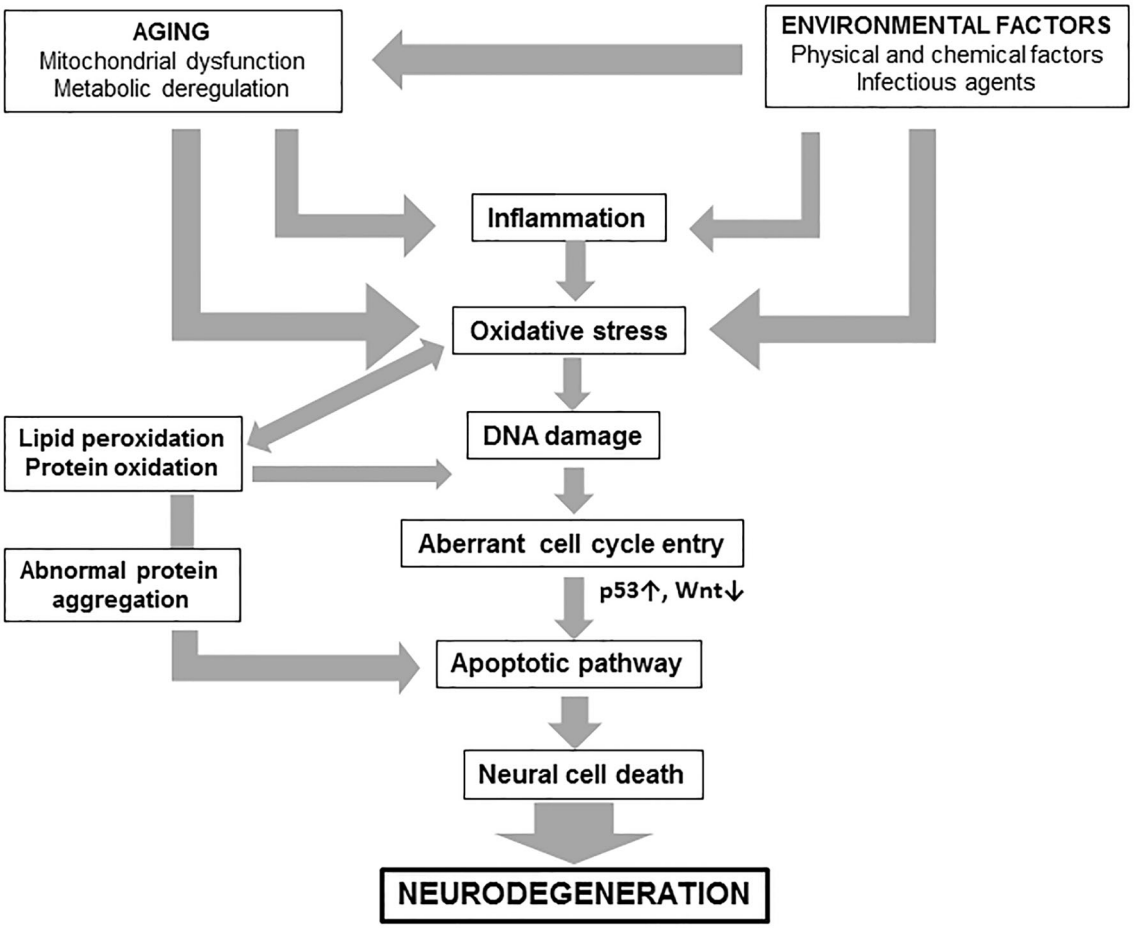


Fig. 4 Schematic representation of the establishment of neurodegeneration, taking in consideration that aging, environmental factors and oxidative stress play a key role in those processes

neurodegeneration and acute neuronal injury (e.g., stroke) (Calabrese et al. 2009; Joseph et al. 2009; Mandel and Youdim 2004; Simonyi et al. 2005).

Polyphenol Antioxidant Properties: Focus on Catechins

The current research on polyphenols is focusing on several possible actions, including health promotion, disease prevention, and the development of therapeutic interventions. However, evidence suggests that the benefits of polyphenols may be greater than currently known; their antioxidant properties can counteract OS induced by free radicals, which is involved in the etiology of a wide range of chronic diseases (Ames and Gold 1991). Polyphenols are secondary metabolites that play a host of general, protective roles (e.g., donation of electrons or hydrogen atoms, free radical scavenging, chelation of metallic ions, UV light-absorbing, inhibition of enzymes involved in the production of free radicals, and antiproliferative agents) and defend plants against microorganisms such as bacteria, fungi, and viruses. They also manage inter-plant relationships and may dictate or modify the plant's relationship with more complex organisms (Kennedy and Wightman 2011; Tahara 2007; Wink 2003). Many of these phytochemicals have been well studied for their abilities to prevent or treat chronic diseases including prevention and treatment of cancer (McCann et al. 2003; Miller and Snyder 2012), cardiovascular disease (Bohn et al. 2012; Vasanthi et al. 2012), obesity (Gonzalez-Castejon and Rodriguez-Casado 2011; Yun 2010), diabetes (Sears and Ricordi 2012), and neurological dysfunctions (Youdim and Joseph 2001). Significant antioxidant properties have been attributed to polyphenols and associated with their capacity to treat chronic diseases (Anderson et al. 2001; Hertog et al. 1993). Antioxidants are compounds that protect cells against the damaging effects of ROS including singlet oxygen, superoxide anion, peroxyl and hydroxyl radicals, and peroxynitrite which result in increased OS and cellular damage (Mattson and Cheng 2006). Antioxidants act by reacting with free radicals, especially ROS, reducing OS.

By definition, free radicals are metastable chemical species that can trap electrons from biomolecules in the immediate surroundings. Antioxidant compounds have distinct mechanisms of action, and some antioxidant polyphenols not only scavenge ROS but also have transition metal chelating activity for species such as ferrous ions (Fe^{2+}) (Obrenovich et al. 2011).

When not effectively scavenged, free radicals may damage biomolecules such as lipids, proteins, and DNA, resulting in abnormalities that may lead to disease (Uddin et al. 2008). Interestingly, several studies have shown that many dietary polyphenolic compounds derived from plants are more effective antioxidants in vitro than powerful well-known antioxidants, such as vitamins E or C, and thus might contribute to protective effects against several diseases in vivo (Jayasri 2009; Rice-Evans et al. 1997). From a historical perspective, studies were more focused on the antioxidant capabilities of carotenoids, vitamins, and minerals. In recent years, this paradigm has changed and the number of studies focused on the effects of dietary polyphenols on human health has considerably increased. Most of those studies strongly support a role for polyphenols in the prevention of degenerative diseases.

Tea catechins are powerful hydrogen-donating antioxidants and free radical scavengers of ROS and RNS (Nanjo et al. 1996; Rice-Evans 1999; Salah et al. 1995). The potent radical scavenging properties of polyphenols have been attributed to the presence of the ortho-3′,4′-dihydroxy moiety in the B ring of their molecule (e.g., catechin, ECG), which participates in electron delocalization and stabilizes the radical form. The gallocatechins possess a trihydroxyl group in the B ring (3′,4′,5-OH) and the gallates contain a galloyl moiety attached to flavan-3-ol at the 3 position (C ring), adding three more hydroxyl groups, as in the case of ECG and EGCG. Both the galloyl moiety and the three hydroxyls in the B ring are suggested to confer better antioxidant activity (Nanjo et al. 1996). White and green tea polyphenols were reported to have a more powerful antioxidant activity than vitamins E and C (Rice-Evans et al. 1995). As discussed, polyphenols are the most abundant antioxidants present in a normal diet with a total intake as high as 1 g/day. This quantity is not only much higher than all other classes of phytochemicals but also all other known dietary antioxidants. For comparative purposes, this is 10 times higher than the intake of vitamin C and 100 times higher than the intake of vitamin E and carotenoids (Scalbert et al. 2005). These compounds are reported to possess several health benefits to the brain, including neuroprotective and neurorescuing properties at very low quantities, such as micromolar or submicromolar concentrations (Mandel et al. 2005). Their effect in the brain is relatively well-known and they are reported to inhibit lipid peroxidation induced in homogenates of brain mitochondrial membranes (Levites et al. 2002) and brain synaptosomes (Guo et al. 1996). Still, many antioxidant compounds, in particular vitamins C, E, some B group vitamins and some polyphenols are known to possess both antioxidant and pro-oxidant properties under certain conditions. The possible use of these antioxidants in therapy should therefore always take into account that they may have labile redox potential (for extensive review (Obrenovich et al. 2011)).

Polyphenols and Neurodegeneration

The brain has a vast array of cognitive and behavioral functions that depend on an intricate network of neurons and supporting glial cells (i.e., astrocytes and microglia). Despite comprising only 2 % of the adult body weight, the brain requires a substantial amount of energy to maintain its function. Changes in the functional integrity or efficiency of energy supply contribute to impairments in brain function, neuronal signaling, and other brain dysfunctions. As discussed, neurodegenerative diseases are suggested to be promoted by OS (Halliwell 2001). There has been a growing interest in pharmacological treatments to counteract the biological decline associated with aging and neurodegenerative diseases to improve quality of life of the elderly. For example, a number of agents have been proposed to slow the progression of AD. Of these, we highlight monoamine oxidase inhibitors, anti-inflammatory and cholinergic agents, estrogens, or neurotrophic factors, and obviously antioxidants (Combs et al. 2000; Emilien et al. 2000; Halliday et al. 2000; Pitchumoni and Doraiswamy 1998; Sramek and Cutler 1999; Youdim and Joseph 2001). Notably, pharmaceutical companies continue to invest in the search for a suitable agent that could be used to counteract the deleterious effects of neurodegenerative disorders. However, there has not been a strong investment in phytochemicals utilization, although they appear to have significant benefits that have yet to be fully exploited. For instance, the increased consumption of tea polyphenols has been reported to possess beneficial effects to brain function(s) (Nunes et al. 2014, 2015). In fact, tea has shown to possess neuroprotective properties for PD, AD, and ischemic damage. One important mechanism for the protective effects of EGCG, the main component in unfermented tea's and in neurodegenerative diseases are its iron-chelating properties (Mandel et al. 2004), and dysregulated iron metabolism may be a central pathological feature of PD (Obrenovich et al. 2011). Most of the studies focused on polyphenols and neurodegeneration are based on tea catechins. It was reported that intracisternal injection of EC could improve intracisternal glucose oxidase-induced memory impairment (Matsuoka et al. 1995). The same

study also reported that intravenous injection of catechin or EC improved brain dysfunction induced by cerebral ischemia. Although these constituents were supplied intravenously, there is also evidence that tea polyphenols can localize within the brain following dietary consumption (Youdim and Joseph 2001) and thus could be available to promote similar actions (Matsuoka et al. 1995). Indeed, tea polyphenols have been reported as possessing neuroprotective properties even at micromolar or submicromolar concentrations (Mandel et al. 2005). Typically there are approximately 150 mg of water-soluble polyphenols in a cup of green tea. The major bioactive polyphenol present in unfermented teas is EGCG, but other polyphenols such as ECG, EGC, and EC are present. These catechins, known to act as antioxidants, may require concentrations substantially higher than those commonly found and available in the body, especially in the brain where they were reported to be present only in the nanomolar range after green tea consumption (Schaffer and Halliwell 2012). Of great interest, epidemiological studies have also provided solid evidence that diets rich in polyphenols may present a high benefit for the human brain function (Commenges et al. 2000; Letenneur et al. 2007). Studies in rodents and in humans with isolated polyphenols (Macready et al. 2009; Maher et al. 2006) or polyphenols-rich foods and plant extracts (e.g., tea, blueberries or pine bark extract) (Macready et al. 2009; Nurk et al. 2009; Ryan et al. 2008) have reported an improvement in memory and cognition. A study with thirty-one volunteers taking a placebo or treated with Teavigo® (a caffeine-free purified and refined tea extract consisting of ~94 % EGCG and ~6 % vitamin C) showed that its consumption increased self-rated calmness and reduced self-rated stress, illustrating that catechin rich extracts may have positive effects on brain function. Other double-blinded, placebo-controlled, crossover study performed in 27 individuals receiving placebo and EGCG showed that a single dose of orally administered EGCG can modify several cerebral blood flow parameters in humans. The results obtained in this study show that, in comparison to placebo, a lower (135 mg) dose of EGCG induces a reduction in cerebral blood flow during the task period (Wightman et al. 2012). Unfortunately, there is a lack of intervention studies focused on the effect of catechins in neurotoxicity and neurodegeneration and the molecular pathways altered by these compounds. Although the mechanisms remain largely unknown, free radical scavenging, metal chelation, and interaction with enzymes, for example, by binding to ATP sites and receptors—modulating their activities—have been suggested as key events for the positive impact of polyphenols on the brain (Schaffer et al. 2006; Spencer 2008, Spencer 2009). Besides the mechanisms already discussed, recent literature provides evidence for a protective role of polyphenols by promoting autophagy. Lately, there is an increasing number of studies showing the pro-autophagic potential of polyphenols (Pallauf and Rimbach 2013; Singletary and Milner 2008). Indeed, there is strong evidence that autophagy can take part of the underlying mechanism of polyphenols action. Data have shown that protein aggregation, neuroinflammation, and ROS-producing dysfunctional mitochondria tend to decrease with well-functioning autophagy (Pallauf and Rimbach 2013). Several studies support an association between autophagy and polyphenols action, since polyphenol-supplemented diets are capable to reduced neuroinflammation in mice (Abraham and Johnson 2009) and have ROS production-reducing effects on mitochondria in a Drosophila PD model (Long et al. 2009), while plant metabolites (including polyphenols) were shown to prolong life span via promotion of autophagy (Morselli et al. 2010; 2011).

Recently, the potential role of polyphenols in regulating human health through epigenetic effects has also become evident, regardless the specific mechanisms still being unclear. Most neurodegenerative diseases are considered complex diseases caused by a variety of factors and may be familial or sporadic in origin, with genetic and environmental factors contributing to their development. Recent studies showed beneficial effects on those diseases via regulation of nuclear factor kappa B (NFKB) expression, chromatin remodeling, through inhibition or activation of histone deacetylases (HDAC) and DNA methyltransferases (DNMT) activities, which in turn can reverse abnormal gene expression (Remely et al. 2015). For instance, some polyphenols such as genistein, myricetin, and quercetin, with a hydroxyl group at positions 5 and 7, caused both inhibition and activation of HDACs and DNMTs depending on experimental conditions (Ayissi et al. 2014; Remely et al. 2015). Notably, bioactive phytochemicals, including EGCG, resveratrol, and curcumin, play important roles as epigenetic modifiers (Li et al. 2011; Martin et al. 2013; Meeran et al. 2010). Thus, eating certain foods that contain bioactive dietary compounds like EGCG can promote epigenetic modifications such as DNA methylation, histone modification, and noncoding RNA. A study conducted by Fang et al. (Fang et al. 2003) showed that EGCG treatment lowered DNA methyltransferase activity in esophageal cancer cells and resulted in the reversal of the hypermethylated state of tumor suppressor genes. Recent studies also suggest that changes in microRNA expression may also be mediated by EGCG and other polyphenols. Moreover, an extensive investigation by Milenkovic and collaborators (Milenkovic et al. 2012) used miRNA microarrays to probe for 567 miRNAs in mice that had been supplemented with nine different polyphenols, including phenolic acids and flavonoids, for 2 weeks. This study showed that there was an average fold change of −2

for downregulated miRNAs and an average fold change of 2.24 for upregulated miRNAs (Milenkovic et al. 2012). These alterations in the epigenome are suggested to aid in the prevention of various age-associated disorders, namely neurodegenerative diseases (Daniel and Tollefsbol 2015).

As discussed, polyphenols are classically described as potent antioxidants, since they have the ability to directly scavenge-free radicals and other reactive species (for a detailed review see Halliwell 2006), at least in vitro (Pannala et al. 1997; Russo et al. 2000; Visioli et al. 1998). However, their in vivo relevance remains a matter of debate. The possible brain effects of polyphenols can also be indirect, through several mechanisms such as (1) activation of a hormetic dose–response and (2) effects on peripheral systems of the body, influencing the CNS functioning (Schaffer and Halliwell 2012). As discussed, the brain is highly vulnerable to OS and thus, sufficient supply of antioxidants to the CNS is pivotal to maintain brain homeostasis (Halliwell 2006; Reiter 1995). It has been proposed that polyphenols can act as antioxidants via two main mechanisms of action (Sandoval-Acuna et al. 2014). The first comprises a direct scavenging action against free radicals or ROS (Amic et al. 2007; Bors et al. 1990), and a favorable induction of endogenous enzymes involved in ROS-removing (e.g., SOD, catalase, and Gpx) and antioxidant-synthesis. The second is linked with a direct inhibitory action of polyphenols on the metal-dependent formation of free radicals (i.e., superoxide anion and hydroxyl radicals) and on ROS-producing enzymes (for review (Sandoval-Acuna et al. 2014)).

Catechins are the major group of flavonoids found in unfermented teas and their antioxidant properties, initially detected in vitro, has led to a growing interest in the potential health benefits of tea consumption (Higdon and Frei 2003). Numerous in vitro studies have focused on tea catechins antioxidant activity against various radicals, including hydroxyl, superoxide anion, peroxyl, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals (Atoui et al. 2005; Tang et al. 2001). It was shown that ECG, EC, and catechin have a peroxyl radical scavenging activity ten times higher than well-known antioxidants such as vitamin C and β-carotene (Nakao et al. 1998). In addition to polyphenols present in tea, EVOO-derived ones have also been studied in recent years. EVOO is becoming more important in daily diets due to its health beneficial effects, most of which are related to its antioxidant content. Their most studied and widely known biological activities, involved in neuroprotection, are free radical scavenging/antioxidant action, lipid peroxidation inhibition, anti-inflammatory, glutathione restoration, and antiapoptotic properties (Khalatbary 2013).

A recent study, using the double transgenic TgCRND8 mice (overexpressing the Swedish and Indiana mutations in the human amyloid precursor protein), examined in vivo effects of 8 weeks dietary supplementation of oleuropein aglycone (OLE) (50 mg/kg of diet) the main polyphenol found in EVOO. This study supported the efficacy of a healthy diet, and the beneficial effects of the Mediterranean diet, which can be traced back to the intake of EVOO and its main polyphenol, OLE. Thus, they strongly suggest that dietary supplementation with OLE may prevent or delay the occurrence of AD and may reduce the severity of its symptoms (Grossi et al. 2013).

The polyphenols antioxidant mechanisms can affect various sub-cellular compartments, and their effect at mitochondrial level was recently recognized as a key mechanism for their action (Schaffer et al. 2012; Smith et al. 2012; Visioli et al. 2011). For instance, resveratrol has been suggested to improve mitochondrial function and to protect against metabolic disease by activating Sirtuin 1 (SIRT1) and PGC-1alpha signaling (Schaffer et al. 2012). Mitochondria are key players in the regulation of cell homeostasis. They are critical for energy production but at the same time, ROS accumulate as by-products of the electron transport chain, causing mitochondrial damage. The most effective mechanism to produce ATP in the cell is via mitochondria, through oxidative phosphorylation (Kelsey et al. 2010). Indeed, 90 % of cellular ATP is generated by the oxidative phosphorylation, making mitochondria also the main generators of cellular ROS, which are produced at complexes I and III of the electron transport chain (ETC). Without ATP, the cell becomes deprived of energy and eventually dies. During this process, oxygen plays an essential role. Although oxygen is essential for energy production by aerobic organism, it also promotes the formation of free radicals, inducing OS. In normal physiological conditions organisms have antioxidant systems that allow a certain degree of protection against free radical toxicity. Thus, OS occurs when there is a high production of oxidants or a low level of antioxidants, resulting in an imbalance between oxidant and antioxidant systems toward an environment rich in free radicals that can cause damage. There are many sources of ROS and RNS (for detail see Fig. 5). Moreover, OS can be extrinsically induced by environmental factors (chemicals, UV light, and infectious organisms, among others) or intrinsically generated by endogenous factors that include the ETC in mitochondria, enzymes (such as NADH oxidase and nitric oxide synthase (NOS) and respiratory bursts from inflammatory cells (Thanan et al. 2015), among others.). The processes of senescence and neurodegeneration that occur in the CNS are suggested to be a consequence of mitochondrial oxidative insults and impaired electron transfer. The accumulation of several oxidation products in neurons during aging strongly suggests and supports that consumption of antioxidant compounds may delay

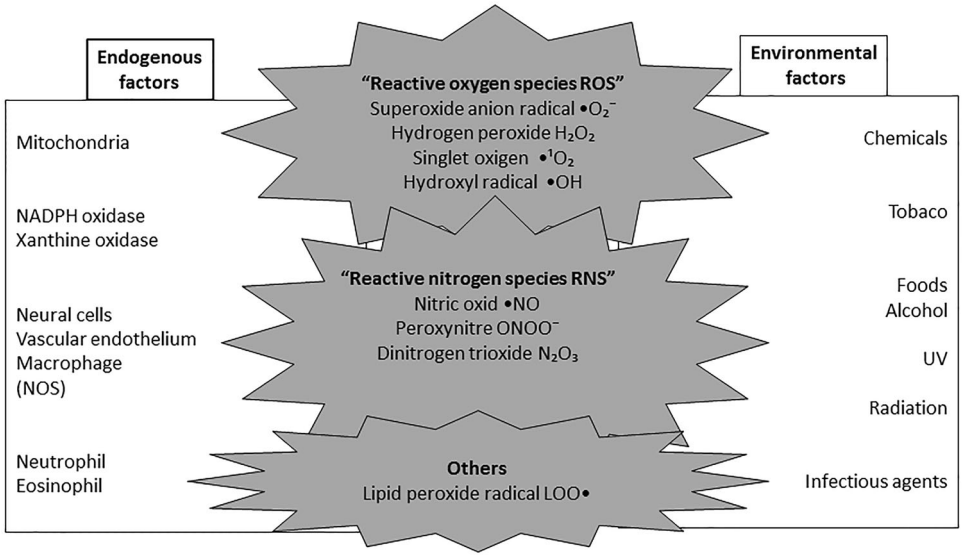


Fig. 5 Schematic representation of several sources for reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the cell. There are different endogenous and environmental factors that end-up in ROS and RNS overproduction including chemicals, UV light, infectious organisms or NADH oxidase, and nitric oxide synthase (NOS), among others

neurodegenerative processes (Assuncao and Andrade 2015). Mitochondria not only represent the major site of superoxide anion radical generation in cells but are also an important target for oxidative action of ROS (Smith et al. 2012). The mitochondrial ETC generates superoxide under physiological conditions, and OS increases ROS production. Additionally, damage of mtDNA appears to alter ETC proteins expression and functioning, causing the production of more superoxide anion radical. Reducing excess amounts of mitochondria-generated superoxide seems important to protect against OS-related diseases (for review Indo et al. 2015). Polyphenols can also act directly as antioxidant in vivo through a ROS-scavenging mechanism, as reported for some of these compounds (i.e., quercetin and EGCG), which have been shown to enter and accumulate within mitochondria (Sandoval-Acuna et al. 2014). Indeed, dysfunction of single mitochondrial enzyme complexes, ROS production, mitochondrial permeability transition pore opening (mPTP), and elevated apoptosis, as well as structural alterations and a diminished mitochondrial content, play a role in brain aging and are believed to be crucial for the onset and progression of neurodegenerative diseases (Bilsland et al. 2008; Casley et al. 2002; Napoli et al. 2006; Schaffer et al. 2012). One of the major relevant effects of oxidative damage is lipid peroxidation, which is essential in the development of neurodegenerative diseases, because polyunsaturated fatty acids are abundant in the lipid bilayers of the brain cells (Subczynski and Hyde 1983). In fact, lipid peroxidation end products were reported to be highly increased in patients with AD (Aluise et al. 2010; Galasko and Montine 2010; Neely and Montine 2002; Reed et al. 2008), PD (Tsang and Chung 2009), and HD (Perez-De La Cruz et al. 2009; Reed 2011). ROS (hydrogen peroxide or superoxide anion radical) formation mainly occurs as a direct result of energy production processes in nearly all tissues of the body, which will inevitably be exposed to their damaging effects. Nevertheless, the effects of ROS can be particularly evident in certain tissues and especially in the brain. When compared with all other tissues undergoing mitochondrial respiration, the brain uses more than 20 % of all oxygen available being the potential for ROS exposure concomitantly increased (Rossi et al. 2008). Moreover, brain tissue-specific reactions such as those involving the enzyme monoamine oxidase also contribute to comparatively high levels of ROS-like hydrogen peroxide (Rossi et al. 2008). Brain is metabolically very active but has reasonably less capacity for cellular regeneration compared to other organs. In normal conditions, and specifically in brain tissue, 1–5 % of the oxygen is converted to ROS (Bhat et al. 2015) which leads to the assumption that the brain is particularly susceptible to ROS damaging effects. Indeed, these values are considerably lower when analyzing the production of ROS by other tissues. A study that measured the production of ROS by intact mitochondria from rat skeletal muscle, heart, and liver showed that only 0.15 % of the oxygen is converted to ROS in those tissues (St-Pierre et al. 2002). Moreover, In AD and PD high levels of ROS-induced damage have been reported within the brain region that undergoes selective neurodegeneration highlighting the relevance of ROS in the onset and progression of those diseases.

In recent years, it has been suggested that polyphenols, acting as antioxidants, decrease ROS levels. For instance, in a study focused on the effects of flavonoid-rich extract from *Rosa laevigata* Michx fruit against hydrogen peroxide-induced damage in PC12 cells, suggested that the flavonoids enhanced positive effects against hydrogen

peroxide-induced oxidative injury by adjusting OS, and controlling apoptosis and inflammation (Liu et al. 2014). Notably, they also diminished intracellular generation of ROS (Liu et al. 2014). Moreover, the efficacy of a number of dietary antioxidants (polyphenols, carotenoids, thiolic compounds, and oligoelements) on the viability of neuronal PC12 cells following nerve growth factor (NGF) deprivation (a model of age-related decrease of neurotrophic support that triggers neuronal loss) has been described (Amara et al. 2015). All dietary antioxidants were able to efficiently support cell viability by reducing ROS levels and restoring mitochondrial function, while preserving neuronal morphology. Furthermore, ROS reduction and neuroprotection during NGF withdrawal were also achieved with defined cocktails of 3–6 different antioxidants at concentrations 5–60 times lower than those used in single treatments, suggesting that their antioxidant activity was preserved even at very low concentrations (Amara et al. 2015).

Polyphenols in Neurodegenerative Diseases

The neuroprotective properties of unfermented teas have been attributed to its high content of phenolic compounds, particularly catechins and other flavan-3-ols, and their antioxidant activity (Nunes et al. 2014). Interestingly, white tea has been proven to possess a strong antioxidant activity, higher than any other type of tea. A recent study described that white tea extract was richer in flavonoids than green tea extract, predominantly EGCG, which is known as one of the most powerful antioxidants and the most pharmacologically active catechin derivative (Dias et al. 2014). Amyloid plaque formation and its toxicity are inhibited by EGCG (Bastianetto et al. 2006). EGCG has other neuroprotective and/or neuromodulator actions, namely protection against hydrogen peroxide-induced toxicity (Okello et al. 2011) and mitochondrial dysfunction related to amyloid toxicity (Dragicevic et al. 2011). In neurons, aggregation of amyloid beta (Aβ) protein stimulates ROS production due to mitochondrial dysfunction, through an *N*-methyl-D-aspartate-dependent pathway. This process is known to be quenched by EGCG, thus protecting against neurodegenerative diseases (He et al. 2011). OS and the associated ROS generation contribute to inflammation and are implicated in the onset of neurodegenerative diseases (Halliwell 2001). Both AD and PD patients show oxidative damage and increased iron accumulation in specific areas of the brain (Riederer et al. 1989). In fact, AD and PD have similarities in pathology, including marked increase in OS, increased lipid peroxidation, reduced mitochondrial activity, increased iron concentration, α-synuclein aggregation, leading to neuronal toxicity, as well as mitochondrial and cytochrome c oxidase malfunction (Perry et al. 2002; Recchia et al. 2004). Resveratrol, the main phenolic compound present in red wine, possesses also many biochemical and pharmacological activities potentially useful for the treatment of neurodegenerative diseases, including ROS scavenging, reduction of inflammation, mitochondrial biogenesis promotion, and caloric restriction (CR) mimicking. SIRT1 and AMPK activation by resveratrol result in upregulation of several protective biological functions (e.g., autophagy) and inhibition of neuronal death by apoptosis (Stefani and Rigacci 2014). There are several clinical trials in progress to further disclose the potential therapeutic effect of resveratrol on cognitive function and cerebral blood flow, in brain aging with mild cognitive impairment (MCI) and AD. There are also some polyphenols that appear to be capable of interfering with enzymatic pathways that lead to the formation of the aggregation-prone Aβ peptides from amyloid precursor protein (APP). EGCG (intraperitoneally injected in APPsw transgenic mice, 20 mg/kg for 60 days) and oleuropein (12.5–50 mM added to the culture medium of HEK293 and SK-NSH neuroblastoma cells, overexpressing and endogenously expressing APP, respectively) promote the nonamyloidogenic α-secretase-mediated APP proteolysis, increasing the production of the *N*-terminal APP cleavage derivative (soluble APP-α), which leads to a decrease in Aβ levels and plaques (Kostomoiri et al. 2013; Rezai-Zadeh et al. 2005).

Polyphenols as Modulators of Intracellular Signaling

Besides the conventional actions discussed above, polyphenols have been consistently reported as modulators of intracellular signaling. Indeed, polyphenols are reported to interact with several neuronal and glial kinase signaling cascades, being the most widely studied the mitogen-activated protein kinases (MAPK), phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB), and target of rapamycin (TOR) signaling (for extensive review (Baptista et al. 2014; Williams and Spencer 2012)). Indeed, polyphenols can directly bind to individual protein kinases and change their phosphorylation state, thus modulating the outcome and physiological function of the signaling events involved (for review (Hou and Kumamoto 2010)). There are some studies showing that polyphenols can directly modify these pathways altering brain function. Resveratrol has been reported to protect against neurodegeneration induced by ischemia through downregulation of the expression of glycogen synthase kinase 3 (GSK-3β) and cyclic adenosine monophosphate (cAMP) response element binding (CREB) proteins, in a mode controlled by PI3K/Akt signaling

(Simao et al. 2012). It was also shown that baicalein, a flavonoid isolated from the roots of *Scutellaria baicalensis* Georgi and *Scutellaria lateriflora* L., protects neurons against ischemia injury, in a mechanism mediated by PI3K/Akt signaling (Liu et al. 2010).

Neurotoxicity is known to be mediated by several signaling molecules, including NFkB, which not only mediates inflammatory processes, but also Aβ toxicity (Valerio et al. 2006). Indeed, activation of NFkB contributes to inflammation and cell death under ischemic conditions (Zhang et al. 2005). Several flavonoids, such as kaempferol, quercetin, acacetin, apigenin and luteolin have shown the capacity to inhibit Aβ1-40 and Aβ1-42 through a downregulation of NFkB pathway (Paris et al. 2011). Others, as the soybean isoflavone, have also been shown to improve learning and memory ability in rats, by inducing a decrease in NFkB activity (Ding et al. 2011). Moreover, resveratrol (Capiralla et al. 2012) and baicalein (Xue et al. 2010) were reported to inhibit Aβ-induced inflammation also by downregulation of NFkB signaling pathway. A preventive effect of silymarin, which is extracted from the seeds of *Silybum marianum* (L.) Gaertn or milk thistle, in cerebral ischemia–reperfusion-induced brain injury in rats, possibly through impairing NFkB activation, was also reported (Hou et al. 2010). Interestingly, quercetin has shown properties that protect the rat brain against OS and hypoxia-induced damage (Patir et al. 2012). Other polyphenols that can be attained by diet, such as catechins and fisetin, were also reported to protect the brain from ischemic and oxidative injuries, by inhibiting NFkB expression (Ashafaq et al. 2012; Gelderblom et al. 2012). The oral administration of resveratrol to humans was reported to reduce OS and inflammatory markers, causing a decrease in NFkB binding activity (Ghanim et al. 2010) and a increase in nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activity (Ghanim et al. 2011).

Peroxisome proliferator-activated receptor gamma (PPAR gamma) signaling is also reported to play a major role in neurodegeneration and cerebral ischemia (Chen et al. 2012). In a study carried out following the occlusion and reperfusion of the middle cerebral artery in rats, PPAR gamma expression and translocation to the nucleus was reported, with the polyphenol baicalein presenting the capacity to prevent those effects (Xu et al. 2010). A resveratrol derivative known as pterostilbene was shown to downregulate the expression of PPAR-α (Chang et al. 2012) in a SAMP8 mouse model, which is a model to examine the pathophysiology of early defects associated with AD (Morley 2002). The encoding of antioxidant proteins is reported to be dependent of Nrf2 signaling (Shin et al. 2012). Several polyphenols have been shown to interact with this pathway. For instance, EC was reported to protect neurons against stroke and OS through an upregulation of Nrf2 signaling (Shah et al. 2010). Resveratrol showed brain protective properties, by increasing the expression of Nrf2 (Ren et al. 2011). It has also been shown that caspase-3 activation in neurons due to OS is blocked by flavonoids (Schroeter et al. 2001; Spencer et al. 2001). Thus, there is strong evidence that the antioxidant properties of polyphenols can be a result of direct but also of indirect actions, particularly by modulating several intracellular signaling pathways (Fig. 6).

Polyphenols can also interact with a range of neurotransmitters and other signaling molecules including $GABA_A$, adenosine, opioid, nicotinic, and receptor tyrosine kinases (Karton et al. 1996; Katavic et al. 2007; Lee et al. 2011; Medina et al. 1998). For instance, resveratrol, hesperetin, and naringenin were reported to have an inhibitory effect in several kinases (Fischer and Lane 2000; Huang et al. 1999). Notably, MEK inhibitor PD98059 has a structural homology with flavonoids (Reiners et al. 1998), illustrating that dietary flavonoids may interact with MEK signaling pathways, changing their biological functions. Indeed, flavonoids are reported to exert their anti-inflammatory effects through regulation of MEK1 and extracellular-signal-regulated kinase (ERK) signaling (Lee et al. 2013). Polyphenols can activate or inhibit ERK, depending on the concentration (e.g., epicatechin) (Kim et al. 2004). In addition, it has been reported that resveratrol inhibits MEK (Rahman et al. 2006). Another crucial event for brain is calcium influx, which is implicated in neuronal death that occurs in most neurodegenerative diseases. Catechins were suggested to up-regulate these calcium fluxes, since they are known to increase the AMPA glutamate receptor subunit Glur2 levels, which is essential to calcium-mediated neuronal events, modulating neurotransmission, plasticity, and synaptogenesis (Isaac et al. 2007; Schroeter et al. 2007). All these events, controlled by polyphenols, provide evidence that protection against neurotoxicity and neurodegeneration described after exposure to these compounds is mediated by the integrated action of signaling pathways crucial for several biological processes.

Polyphenols Absorption and Bioavailability

Dietary polyphenols present a wide range of biological activities. Besides the mechanisms discussed above, these compounds are also reported to interact with autoimmune response (Chen 2011), metal ion chelation (Mandel et al. 2007), prions (Rambold et al. 2008), acetylcholestinesterase activity (Papandreou et al. 2009), autophagy (Pallauf and Rimbach 2013), and several other factors. The beneficial effects of polyphenols are highly evidenced, and since they can be attained from plant foods, it has been suggested that they may be clinically very

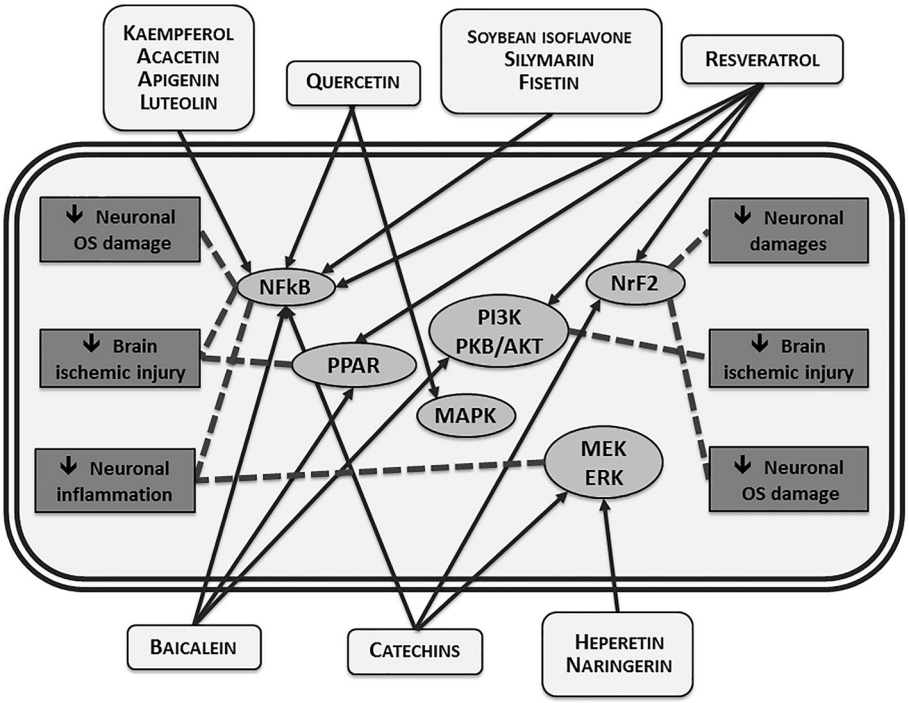


Fig. 6 Schematic representation of mechanisms underlying the biological effects of polyphenols as modulators of intracellular signaling. Polyphenols, such as resveratrol, quercetin and baicalein, activate cellular stress-response pathways resulting in the upregulation of neuroprotective genes. For example, ERK can activate the nuclear factor erythroid 2-related factor 2 (Nrf2). In addition, polyphenols can also regulate the transcription factor NF-κB, which can mediate adaptive cellular stress responses by reducing the expression of inflammatory cytokines. NFkB activation also contributes to inflammation and cell death under ischemic conditions

relevant to counteract or avoid neurotoxicity and neurodegenerative diseases. Interestingly, several flavonoids and other polyphenols have been shown to possess hormone-like properties due to their capacity to bind estrogen receptors (Louw et al. 2013) and affinity to testosterone receptors (Nifli et al. 2005). Those properties have been overlooked and should be taken in consideration when assessing the safety and health applications of polyphenols. Moreover, dietary supplementation of polyphenols to present any effect on the brain must first cross the BBB. It has been already shown that some polyphenols are retained, becoming more concentrated, in the neural tissue than in plasma (Kalt et al. 2008; Milbury and Kalt 2010; Talavera et al. 2005). Several dietary flavones, such as hesperetin and naringenin, were already shown to cross the BBB (Youdim et al. 2003, 2004a, 2004b), and it has been suggested that the penetration of these compounds is dependent on their lipophilicity (Youdim et al. 2003). Polyphenols can also cross BBB through specific efflux transporters, particularly *P*-glycoprotein, which has already been reported to possess different affinity fluxes according with the polyphenol present (Youdim et al. 2004a). Interestingly, it has also been suggested the existence of binding sites at brain plasma membrane with high affinity for these compounds (Han et al. 2006). Nevertheless, this remains a matter of debate and these sites have not yet been characterized.

The parameters of absorption, bioavailability, biodistribution, and metabolism of polyphenols are not entirely understood, but in general it appears that some polyphenols are bioactive upon absorption through the intestine in their native or modified form. It is well established that polyphenols are metabolized by intestinal flora and their metabolites can also be absorbed. Natural polyphenols are frequently in conjugated form, with one or more sugars, generally bound to the hydroxyl groups. Their physical, chemical, or biological properties are influenced by glycosylation, which also defines natural polyphenols absorption by the small intestine. These processes are also affected by their molecular size, degree of polymerization (tannin formation), binding to proteins, or dietary fibers, and solubility (Rahman et al. 2006). It is very important to highlight that the systemic availability of natural polyphenols can be very low after oral administration, since most of them are metabolized by intestinal enzymes. Absorption by the gut epithelium leads to biotransformation by the liver, where polyphenols are methylated and/or conjugated with glucuronic acid or sulfate (Rahman et al. 2006). For instance, studies with radio-labeled resveratrol in mice have revealed that resveratrol is distributed to all organs and remained detectable in the lung, spleen, heart, brain, and testis for up to 6 h (Vitrac et al. 2003). Bioavailability of catechins is also very changeable. EGCG is the only known polyphenol present in plasma, with a large proportion (77–90 %) in a free form (Chen et al. 1997). The other catechins are highly conjugated with glucuronic acid and/or sulfate groups, and it has been described that galloylation of catechins reduces their

absorption (Van Amelsvoort et al. 2001). It was reported that only EGC was methylated and that 4-*O*-methyl-EGC accounted for 30–40 % of the total metabolites of EGC (Van Amelsvoort et al. 2001). These aspects are very important when extrapolating the effects observed in the in vitro studies to the in vivo brain situation. Therefore, the ability of these compounds to cross the BBB that has been mentioned above, and which tightly controls the influx to the brain of metabolites and nutrients as well as drugs, is of utmost importance for the relevance of polyphenols present in diet to the aging brain.

Therefore, it is well established that only a small fraction of polyphenols is absorbed, with the majority being hydrolyzed or metabolized before absorption (Bolca et al. 2013; Faria et al. 2014), illustrating that it is crucial to determine the mechanisms of action of these compounds according to their concentrations and the compounds resultant from their metabolization. This is often overlooked, but is of particular relevance, since it has been shown that the conjugated forms of polyphenols and their derivatives have similar, if not greater, bioactivity and may interact with the same signaling pathways (Chiou et al. 2014; Monagas et al. 2010).

Conclusion

Thus, to assess if polyphenols are in fact strong dietary agents against neurotoxicity and neurodegeneration, it is pivotal to study the biotransformation of these compounds and the biological activity of their metabolites. More studies are needed to go far beyond the conventional approach of using specific representatives of polyphenol families. Dietary intervention studies in mammals, including humans, provided compelling evidence that polyphenols can improve memory and learning by protecting the brain from neurotoxicity, enhancing neuronal function and stimulating a certain degree of neuronal regeneration (Galli et al. 2002; Haque et al. 2006; Kuriyama et al. 2006). Nevertheless, the molecular mechanisms responsible for such effects remain largely unknown. Moreover, it must be noted that safety issues may arise depending on the polyphenols concentration obtained from food supplements. These are not controlled as medicinal drugs, and so can be toxic (Murakami 2014). Thus, further studies are needed to allow us a wider perspective on the bioavailability, biotransformation, synergism with other dietary compounds, safety, pleiotropic effects, specific molecular targets, interactions, concentration-dependent effects, and toxicity of dietary polyphenols, which may allow us to evaluate their real potential as a dietary strategy against neurotoxicity and neurodegeneration.

In fact, there are still doubts about if some antioxidants could be potentially harmful to health, since an increase in glycation-mediated protein damage (carbonyl stress) has been reported in some cases (Obrenovich et al. 2010). Despite their beneficial health effects, polyphenols have also been shown to have adverse effects. The co-administration of natural products, namely polyphenols, along with conventional medicines can lead to a modified bioavailability and cause important changes of metabolic pathways, leading to therapeutic inefficacy and increased risk of toxicity (Margina et al. 2015). Antioxidant activity of polyphenols constitutes their most important property and also the most discussed (Boots et al. 2008; Margina et al. 2015; Spanou et al. 2012; Stagos et al. 2012). Nevertheless, flavonoids (like many other antioxidants) can also act, under certain circumstances, as pro-oxidants, for example, in systems containing redox-active metals (copper, iron, etc.). In vivo, most transition metal ions are sequestered in forms unable to catalyze free radical reactions. Under specific conditions, this situation can be modified, as very low levels of free copper ions may be released following tissue injury (e.g., atherosclerotic lesions) and possibly hepatic Cu(II) overload diseases (Wilson disease), thereby being able to promote pro-oxidant effects in association with dietary flavonoids (Galati and O'Brien 2004; Halliwell and Gutteridge 1990; Margina et al. 2015; Smith et al. 1992). Some individual flavonoids, for example quercetin, particularly at high-dose levels, have potentially toxic effects including pro-oxidant activity, which could be related to mutagenicity and mitochondrial toxicity. It has been shown that quercetin efficiently protects against hydrogen peroxide-induced DNA damage in rat lung epithelial (RLE) cells by a reduction in glutathione (GSH) level, an increase in lactate dehydrogenase (LDH) leakage, as well as an increase of cytosolic-free calcium concentration (Boots et al. 2008, 2007), thus acting as a toxicant. This conversion of quercetin into a potential toxicant, while offering protection by scavenging ROS, has been referred as "the quercetin paradox" (Boots et al. 2007). On the other hand, resveratrol has demonstrated antitumor action (Apostolou et al. 2013). It has been shown that resveratrol reverses the multidrug resistance of cancer cells, through downregulation of the MDR-1 gene and P-glycoprotein expression levels, enhancing the cytotoxicity of doxorubicin within solid tumor cells (MCF-7) (Huang et al. 2014; Kim et al. 2014b). Interestingly, some authors claim that the possible pro-oxidant action of some polyphenols is a potential mechanism for their beneficial effects. One example is EGCG, which reduces oxygen to yield hydrogen peroxide, thus promoting apoptosis and exerting cytotoxic activity against bacteria (Nakagawa et al. 2004). Nevertheless, the degree to which polyphenols are able to act as anti- or pro-oxidants in vivo is not yet

well understood and remains a matter of debate (Prochazkova et al. 2011). This will remain a hot topic of research for the years to come.

Acknowledgments This work was supported by the Portuguese "Fundação para a Ciência e a Tecnologia"—FCT: SA (SFRH/BD/112012/2015), MGA (SFRH/BPD/80451/2011 and PTDC/BIM-MET/4712/2014), PFO (SFRH/BPD/108837/2015), CICS-UBI (Pest-C/SAU/UI0709/2014) and UMIB (Pest-OE/SAU/UI0215/2014) were co-funded by FEDER via Programa Operacional Fatores de Competitividade-COMPETE/QREN & FSE and POPH funds. The authors are grateful to Susana Barber, PhD, for professional English proof-reading and linguistic suggestions.

References

Abraham J, Johnson RW (2009) Consuming a diet supplemented with resveratrol reduced infection-related neuroinflammation and deficits in working memory in aged mice. Rejuvenation Res 12:445–453

Aluise CD, Robinson RA, Beckett TL, Murphy MP, Cai J, Pierce WM, Markesbery WR, Butterfield DA (2010) Preclinical Alzheimer disease: brain oxidative stress Abeta peptide and proteomics. Neurobiol Dis 39:221–228

Amara F, Berbenni M, Fragni M, Leoni G, Viggiani S, Ippolito VM, Larocca M, Rossano R, Alberghina L, Riccio P, Colangelo AM (2015) Neuroprotection by cocktails of dietary antioxidants under conditions of nerve growth factor deprivation. Oxidative Med Cell Longev 2015:217258

Ames BN, Gold LS (1991) Endogenous mutagens and the causes of aging and cancer. Mutat Res 250:3–16

Amic D, Davidovic-Amic D, Beslo D, Rastija V, Lucic B, Trinajstic N (2007) SAR and QSAR of the antioxidant activity of flavonoids. Curr Med Chem 14:827–845

Anderson KJ, Teuber SS, Gobeille A, Cremin P, Waterhouse AL, Steinberg FM (2001) Walnut polyphenolics inhibit in vitro human plasma and LDL oxidation. J Nutr 131:2837–2842

Apostolou A, Stagos D, Galitsiou E, Spyrou A, Haroutounian S, Portesis N, Trizoglou I, Wallace Hayes A, Tsatsakis AM, Kouretas D (2013) Assessment of polyphenolic content, antioxidant activity, protection against ROS-induced DNA damage and anticancer activity of *Vitis vinifera* stem extracts. Food Chem Toxicol 61:60–68

Aseervatham GS, Sivasudha T, Jeyadevi R, Arul Ananth D (2013) Environmental factors and unhealthy lifestyle influence oxidative stress in humans–an overview. Environ Sci Pollut Res Int 20:4356–4369

Ashafaq M, Raza SS, Khan MM, Ahmad A, Javed H, Ahmad ME, Tabassum R, Islam F, Siddiqui MS, Safhi MM, Islam F (2012) Catechin hydrate ameliorates redox imbalance and limits inflammatory response in focal cerebral ischemia. Neurochem Res 37:1747–1760

Assuncao M, Andrade JP (2015) Protective action of green tea catechins in neuronal mitochondria during aging. Front Biosci (Landmark Edition) 20:247–262

Atoui AK, Mansouri A, Boskou G, Kefalas P (2005) Tea and herbal infusions: their antioxidant activity and phenolic profile. Food Chem 89:27–36

Ayissi VB, Ebrahimi A, Schluesenner H (2014) Epigenetic effects of natural polyphenols: a focus on SIRT1-mediated mechanisms. Mol Nutr Food Res 58:22–32

Baptista FI, Henriques AG, Silva AM, Wiltfang J, da Cruz e Silva OA (2014) Flavonoids as therapeutic compounds targeting key proteins involved in Alzheimer's disease. ACS Chem Neurosci 5:83–92

Bastianetto S, Yao ZX, Papadopoulos V, Quirion R (2006) Neuroprotective effects of green and black teas and their catechin gallate esters against beta-amyloid-induced toxicity. Eur J Neurosci 23:55–64

Basu A, Sanchez K, Leyva MJ, Wu M, Betts NM, Aston CE, Lyons TJ (2010) Green tea supplementation affects body weight Lipids, and lipid peroxidation in obese subjects with metabolic syndrome. J Am Coll Nutr 29:31–40

Bhat AH, Dar KB, Anees S, Zargar MA, Masood A, Sofi MA, Ganie SA (2015) Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight. Biomed Pharmacother 74:101–110

Bilsland LG, Nirmalananthan N, Yip J, Greensmith L, Duchen MR (2008) Expression of mutant SOD1 in astrocytes induces functional deficits in motor neuron mitochondria. J Neurochem 107:1271–1283

Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A, Leschik-Bonnet E, Muller MJ, Oberritter H, Schulze M, Stehle P, Watzl B (2012) Critical review: vegetables and fruit in the prevention of chronic diseases. Eur J Nutr 51:637–663

Bohn SK, Ward NC, Hodgson JM, Croft KD (2012) Effects of tea and coffee on cardiovascular disease risk. Food Funct 3:575–591

Bolca S, Van de Wiele T, Possemiers S (2013) Gut metabotypes govern health effects of dietary polyphenols. Curr Opin Biotechnol 24:220–225

Boots AW, Li H, Schins RP, Duffin R, Heemskerk JW, Bast A, Haenen GR (2007) The quercetin paradox. Toxicol Appl Pharmacol 222:89–96

Boots AW, Haenen GR, Bast A (2008) Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol 585:325–337

Bors W, Heller W, Michel C, Saran M (1990) Flavonoids as antioxidants: determination of radical-scavenging efficiencies. Methods Enzymol 186:343

Braicu C, Ladomery MR, Chedea VS, Irimie A, Berindan-Neagoe I (2013) The relationship between the structure and biological actions of green tea catechins. Food Chem 141:3282–3289

Calabrese V, Cornelius C, Mancuso C, Barone E, Calafato S, Bates T, Rizzarelli E, Kostova AT (2009) Vitagenes, dietary antioxidants and neuroprotection in neurodegenerative diseases. Front Biosci 14:376–397

Cantuti-Castelvetri I, Shukitt-Hale B, Joseph JA (2000) Neurobehavioral aspects of antioxidants in aging. Int J Dev Neurosci 18:367–381

Capiralla H, Vingtdeux V, Zhao H, Sankowski R, Al-Abed Y, Davies P, Marambaud P (2012) Resveratrol mitigates lipopolysaccharide- and Abeta-mediated microglial inflammation by inhibiting the TLR4/NF-kappaB/STAT signaling cascade. J Neurochem 120:461–472

Casley CS, Land JM, Sharpe MA, Clark JB, Duchen MR, Canevari L (2002) Beta-amyloid fragment 25-35 causes mitochondrial dysfunction in primary cortical neurons. Neurobiol Dis 10:258–267

Chang J, Rimando A, Pallas M, Camins A, Porquet D, Reeves J, Shukitt-Hale B, Smith MA, Joseph JA, Casadesus G (2012) Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease. Neurobiol Ageing 33:2062–2071

Chen S (2011) Natural products triggering biological targets–a review of the anti-inflammatory phytochemicals targeting the arachidonic acid pathway in allergy asthma and rheumatoid arthritis. Curr Drug Targets 12:288–301

Chen A, Zhang L (2003) The antioxidant (−)-epigallocatechin-3-gallate inhibits rat hepatic stellate cell proliferation in vitro by blocking the tyrosine phosphorylation and reducing the gene

expression of platelet-derived growth factor-beta receptor. J Biol Chem 278:23381–23389
Chen L, Lee MJ, Li H, Yang CS (1997) Absorption, distribution, elimination of tea polyphenols in rats. Drug Metab Dispos 25:1045–1050
Chen YC, Wu JS, Tsai HD, Huang CY, Chen JJ, Sun GY, Lin TN (2012) Peroxisome proliferator-activated receptor gamma (PPAR-gamma) and neurodegenerative disorders. Mol Neurobiol 46:114–124
Chiou Y-S, Wu J-C, Huang Q, Shahidi F, Wang Y-J, Ho C-T, Pan M-H (2014) Metabolic and colonic microbiota transformation may enhance the bioactivities of dietary polyphenols. J Funct Foods 7:3–25
Chun OK, Chung SJ, Song WO (2007) Estimated dietary flavonoid intake and major food sources of U.S. adults. J Nutr 137:1244–1252
Chyu KY, Babbidge SM, Zhao X, Dandillaya R, Rietveld AG, Yano J, Dimayuga P, Cercek B, Shah PK (2004) Differential effects of green tea-derived catechin on developing versus established atherosclerosis in apolipoprotein E-null mice. Circulation 109:2448–2453
Combs CK, Johnson DE, Karlo JC, Cannady SB, Landreth GE (2000) Inflammatory mechanisms in Alzheimer's disease: inhibition of β-amyloid-stimulated proinflammatory responses and neurotoxicity by PPARγ agonists. J Neurosci 20:558–567
Commenges D, Scotet V, Renaud S, Jacqmin-Gadda H, Barberger-Gateau P, Dartigues JF (2000) Intake of flavonoids and risk of dementia. Eur J Epidemiol 16:357–363
Daniel M, Tollefsbol TO (2015) Epigenetic linkage of aging, cancer and nutrition. J Exp Biol 218:59–70
de Tommaso M, Serpino C, Sciruicchio V (2011) Management of Huntington's disease: role of tetrabenazine. Therapeutics Clin Risk Manag 7:123–129
Dewick PM (2002) Medicinal natural products: a biosynthetic approach. Wiley, New York
Dias T, Tomás G, Teixeira N, Alves M, Oliveira P, Silva B (2013) White tea (*Camellia sinensis* (L.)): antioxidant properties and beneficial health effects. Int J Food Sci Nutr Diet 2:1–15
Dias TR, Alves MG, Tomas GD, Socorro S, Silva BM, Oliveira PF (2014) White tea as a promising antioxidant medium additive for sperm storage at room temperature: a comparative study with green tea. J Agric Food Chem 62:608–617
Ding BJ, Ma WW, He LL, Zhou X, Yuan LH, Yu HL, Feng JF, Xiao R (2011) Soybean isoflavone alleviates beta-amyloid 1-42 induced inflammatory response to improve learning and memory ability by down regulation of Toll-like receptor 4 expression and nuclear factor-kappaB activity in rats. Int J Dev Neurosci 29:537–542
Doughari JH (2012) Phytochemicals: extraction methods, basic structures and mode of action as potential chemotherapeutic agents. In: Rao DV (ed) Phytochemicals—a global perspective of their role in nutrition and health. INTECH Open Access Publisher, Rijeka, pp 283–359
Dragicevic N, Smith A, Lin X, Yuan F, Copes N, Delic V, Tan J, Cao C, Shytle RD, Bradshaw PC (2011) Green tea epigallocatechin-3-gallate (EGCG) and other flavonoids reduce Alzheimer's amyloid-induced mitochondrial dysfunction. J Alzheimer's Dis 26:507–521
Driver JA (2014) Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence. Biogerontology 15:547–557
Emilien G, Beyreuther K, Masters CL, Maloteaux JM (2000) Prospects for pharmacological intervention in Alzheimer disease. Arch Neurol 57:454–459
Fang MZ, Wang Y, Ai N, Hou Z, Sun Y, Lu H, Welsh W, Yang CS (2003) Tea polyphenol (−)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. Cancer Res 63:7563–7570
Faria A, Pestana D, Teixeira D, Azevedo J, De Freitas V, Mateus N, Calhau C (2010) Flavonoid transport across RBE4 cells: a blood-brain barrier model. Cell Mol Biol Lett 15:234–241
Faria A, Fernandes I, Norberto S, Mateus N, Calhau C (2014) Interplay between anthocyanins and gut microbiota. J Agric Food Chem 62:6898–6902
Fischer PM, Lane DP (2000) Inhibitors of cyclin-dependent kinases as anti-cancer therapeutics. Curr Med Chem 7:1213–1245
Fresco P, Borges F, Diniz C, Marques MP (2006) New insights on the anticancer properties of dietary polyphenols. Med Res Rev 26:747–766
Galasko D, Montine TJ (2010) Biomarkers of oxidative damage and inflammation in Alzheimer's disease. Biomark Med 4:27–36
Galati G, O'Brien PJ (2004) Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. Free Radic Biol Med 37:287–303
Galli RL, Shukitt-Hale B, Youdim KA, Joseph JA (2002) Fruit polyphenolics and brain aging: nutritional interventions targeting age-related neuronal and behavioral deficits. Ann N Y Acad Sci 959:128–132
Gelderblom M, Leypoldt F, Lewerenz J, Birkenmayer G, Orozco D, Ludewig P, Thundyil J, Arumugam TV, Gerloff C, Tolosa E, Maher P, Magnus T (2012) The flavonoid fisetin attenuates postischemic immune cell infiltration, activation and infarct size after transient cerebral middle artery occlusion in mice. J Cereb Blood Flow Metab 32:835–843
Ghanim H, Sia CL, Abuaysheh S, Korzeniewski K, Patnaik P, Marumganti A, Chaudhuri A, Dandona P (2010) An antiinflammatory and reactive oxygen species suppressive effects of an extract of *Polygonum cuspidatum* containing resveratrol. J Clin Endocrinol Metab 95:E1–E8
Ghanim H, Sia CL, Korzeniewski K, Lohano T, Abuaysheh S, Marumganti A, Chaudhuri A, Dandona P (2011) A resveratrol and polyphenol preparation suppresses oxidative and inflammatory stress response to a high-fat, high-carbohydrate meal. J Clin Endocrinol Metab 96:1409–1414
Giordano S, Darley-Usmar V, Zhang J (2014) Autophagy as an essential cellular antioxidant pathway in neurodegenerative disease. Redox Biol 2:82–90
Gonzalez-Castejon M, Rodriguez-Casado A (2011) Dietary phytochemicals and their potential effects on obesity: a review. Pharmacol Res 64:438–455
Grossi C, Rigacci S, Ambrosini S, Ed Dami T, Luccarini I, Traini C, Failli P, Berti A, Casamenti F, Stefani M (2013) The polyphenol oleuropein aglycone protects TgCRND8 mice against Ass plaque pathology. PLoS One 8:e71702
Guo Q, Zhao B, Li M, Shen S, Xin W (1996) Studies on protective mechanisms of four components of green tea polyphenols against lipid peroxidation in synaptosomes. Biochim Biophys Acta 1304:210–222
Haile WB, Wu J, Echeverry R, Wu F, An J, Yepes M (2012) Tissue-type plasminogen activator has a neuroprotective effect in the ischemic brain mediated by neuronal TNF-alpha. J Cereb Blood Flow Metab 32:57–69
Halliday G, Robinson SR, Shepherd C, Kril J (2000) Alzheimer's disease and inflammation: a review of cellular and therapeutic mechanisms. Clin Exp Pharmacol Physiol 27:1–8
Halliwell B (2001) Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. Drugs Aging 18:685–716
Halliwell B (2006) Oxidative stress and neurodegeneration: where are we now? J Neurochem 97:1634–1658
Halliwell B, Gutteridge JM (1990) The antioxidants of human extracellular fluids. Arch Biochem Biophys 280:1–8

Han YS, Bastianetto S, Dumont Y, Quirion R (2006) Specific plasma membrane binding sites for polyphenols, including resveratrol, in the rat brain. J Pharmacol Exp Ther 318:238–245

Hansen BG, Halkier BA (2005) New insight into the biosynthesis and regulation of indole compounds in *Arabidopsis thaliana*. Planta 221:603–606

Haque AM, Hashimoto M, Katakura M, Tanabe Y, Hara Y, Shido O (2006) Long-term administration of green tea catechins improves spatial cognition learning ability in rats. J Nutr 136:1043–1047

Hasler CM, Blumberg JB (1999) Phytochemicals: biochemistry and physiology. Introduction. J Nutr 129:756s–757s

He Y, Cui J, Lee JC, Ding S, Chalimoniuk M, Simonyi A, Sun AY, Gu Z, Weisman GA, Wood WG, Sun GY (2011) Prolonged exposure of cortical neurons to oligomeric amyloid-beta impairs NMDA receptor function via NADPH oxidase-mediated ROS production: protective effect of green tea (−)-epigallocatechin-3-gallate. ASN Neuro 3:e00050

Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D (1993) Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen elderly study. Lancet 342:1007–1011

Higdon JV, Frei B (2003) Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. Crit Rev Food Sci Nutr 43:89–143

Ho L, Sharma N, Blackman L, Festa E, Reddy G, Pasinetti GM (2005) From proteomics to biomarker discovery in Alzheimer's disease. Brain Res Rev 48:360–369

Hollman PC, Katan MB (1999) Health effects and bioavailability of dietary flavonols. Free Radic Res 31(Suppl):S75–S80

Hooper PL, Hooper PL, Tytell M, Vigh L (2010) Xenohormesis: health benefits from an eon of plant stress response evolution. Cell stress Chaperones 15:761–770

Hou DX, Kumamoto T (2010) Flavonoids as protein kinase inhibitors for cancer chemoprevention: direct binding and molecular modeling. Antioxid Redox Signal 13:691–719

Hou YC, Liou KT, Chern CM, Wang YH, Liao JF, Chang S, Chou YH, Shen YC (2010) Preventive effect of silymarin in cerebral ischemia-reperfusion-induced brain injury in rats possibly through impairing NF-kappaB and STAT-1 activation. Phytomedicine 17:963–973

Howitz KT, Sinclair DA (2008) Xenohormesis: sensing the chemical cues of other species. Cell 133:387–391

Huang YT, Hwang JJ, Lee PP, Ke FC, Huang JH, Huang CJ, Kandaswami C, Middleton E Jr, Lee MT (1999) Effects of luteolin and quercetin, inhibitors of tyrosine kinase, on cell growth and metastasis-associated properties in A431 cells overexpressing epidermal growth factor receptor. Br J Pharmacol 128:999–1010

Huang F, Wu XN, Chen J, Wang WX, Lu ZF (2014) Resveratrol reverses multidrug resistance in human breast cancer doxorubicin-resistant cells. Exp Ther Med 7:1611–1616

Indo HP, Yen HC, Nakanishi I, Matsumoto K, Tamura M, Nagano Y, Matsui H, Gusev O, Cornette R, Okuda T, Minamiyama Y, Ichikawa H, Suenaga S, Oki M, Sato T, Ozawa T, Clair DK, Majima HJ (2015) A mitochondrial superoxide theory for oxidative stress diseases and aging. J Clin Biochem Nutr 56:1–7

Isaac JT, Ashby MC, McBain CJ (2007) The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. Neuron 54:859–871

Ischiropoulos H, Beckman JS (2003) Oxidative stress and nitration in neurodegeneration: cause, effect, or association? J Clin Investig 111:163–169

Jayasri MA (2009) A report on the antioxidant activity of leaves and rhizomes of *Costus pictus* D. Don. Int J Integr Biol 5:20–26

Jellinger KA (2006) Alzheimer 100—highlights in the history of Alzheimer research. J Neural Transm 113:1603–1623

Johannot L, Somerset SM (2006) Age-related variations in flavonoid intake and sources in the Australian population. Public Health Nutr 9:1045–1054

Joseph J, Cole G, Head E, Ingram D (2009) Nutrition, brain aging, and neurodegeneration. J Neurosci 29:12795–12801

Kalt W, Blumberg JB, McDonald JE, Vinqvist-Tymchuk MR, Fillmore SA, Graf BA, O'Leary JM, Milbury PE (2008) Identification of anthocyanins in the liver, eye, and brain of blueberry-fed pigs. J Agric Food Chem 56:705–712

Karton Y, Jiang JL, Ji XD, Melman N, Olah ME, Stiles GL, Jacobson KA (1996) Synthesis and biological activities of flavonoid derivatives as A3 adenosine receptor antagonists. J Med Chem 39:2293–2301

Katavic PL, Lamb K, Navarro H, Prisinzano TE (2007) Flavonoids as opioid receptor ligands: identification and preliminary structure-activity relationships. J Nat Prod 70:1278–1282

Kelsey NA, Wilkins HM, Linseman DA (2010) Nutraceutical antioxidants as novel neuroprotective agents. Molecules 15:7792–7814

Kennedy DO, Wightman EL (2011) Herbal extracts and phytochemicals: plant secondary metabolites and the enhancement of human brain function. Adv Nutr 2:32–50

Khalatbary AR (2013) Olive oil phenols and neuroprotection. Nutr Neurosci 16:243–249

Kim JA (2008) Mechanisms underlying beneficial health effects of tea catechins to improve insulin resistance and endothelial dysfunction. Endocr Metab Immune Disord Drug Targets 8:82–88

Kim MJ, Ryu GR, Kang JH, Sim SS, Min DS, Rhie DJ, Yoon SH, Hahn SJ, Jeong IK, Hong KJ, Kim MS, Jo YH (2004) Inhibitory effects of epicatechin on interleukin-1beta-induced inducible nitric oxide synthase expression in RINm5F cells and rat pancreatic islets by down-regulation of NF-kappaB activation. Biochem Pharmacol 68:1775–1785

Kim JA, Formoso G, Li Y, Potenza MA, Marasciulo FL, Montagnani M, Quon MJ (2007) Epigallocatechin gallate, a green tea polyphenol, mediates NO-dependent vasodilation using signaling pathways in vascular endothelium requiring reactive oxygen species and Fyn. J Biol Chem 282:13736–13745

Kim HS, Montana V, Jang HJ, Parpura V, Kim JA (2013) Epigallocatechin gallate (EGCG) stimulates autophagy in vascular endothelial cells: a potential role for reducing lipid accumulation. J Biol Chem 288:22693–22705

Kim HS, Quon MJ, Kim JA (2014a) New insights into the mechanisms of polyphenols beyond antioxidant properties; lessons from the green tea polyphenol, epigallocatechin 3-gallate. Redox Biol 2:187–195

Kim TH, Shin YJ, Won AJ, Lee BM, Choi WS, Jung JH, Chung HY, Kim HS (2014b) Resveratrol enhances chemosensitivity of doxorubicin in multidrug-resistant human breast cancer cells via increased cellular influx of doxorubicin. Biochim Biophys Acta 1840:615–625

Kostomoiri M, Fragkouli A, Sagnou M, Skaltsounis LA, Pelecanou M, Tsilibary EC, Tzinia AK (2013) Oleuropein, an anti-oxidant polyphenol constituent of olive promotes alpha-secretase cleavage of the amyloid precursor protein (AbetaPP). Cell Mol Neurobiol 33:147–154

Kuriyama S, Hozawa A, Ohmori K, Shimazu T, Matsui T, Ebihara S, Awata S, Nagatomi R, Arai H, Tsuji I (2006) Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project 1. Am J Clin Nutr 83:355–361

Kurland LT (1988) Amyotrophic lateral sclerosis and Parkinson's disease complex on Guam linked to an environmental neurotoxin. Trends Neurosci 11:51–54

Lamming DW, Wood JG, Sinclair DA (2004) Small molecules that regulate lifespan: evidence for xenohormesis. Mol Microbiol 53:1003–1009

Lampl C, You X, Limmroth V (2012) Weekly IM interferon beta-1a in multiple sclerosis patients over 50 years of age. Eur J Neurol 19:142–148

Lee BH, Choi SH, Shin TJ, Pyo MK, Hwang SH, Lee SM, Paik HD, Kim HC, Nah SY (2011) Effects of quercetin on alpha9alpha10 nicotinic acetylcholine receptor-mediated ion currents. Eur J Pharmacol 650:79–85

Lee WK, Chung KW, Kim GH, Kim SJ (2013) Gallotannin causes differentiation and inflammation via ERK1/2 and p38 kinase pathways in rabbit articular chondrocytes. Mol Med Rep 7:701–707

Leonov A, Arlia-Ciommo A, Piano A, Svistkova V, Lutchman V, Medkour Y, Titorenko VI (2015) Longevity extension by phytochemicals. Molecules 20:6544–6572

Letenneur L, Proust-Lima C, Le Gouge A, Dartigues JF, Barberger-Gateau P (2007) Flavonoid intake and cognitive decline over a 10-year period. Am J Epidemiol 165:1364–1371

Levites Y, Youdim MB, Maor G, Mandel S (2002) Attenuation of 6-hydroxydopamine (6-OHDA)-induced nuclear factor-kappaB (NF-kappaB) activation and cell death by tea extracts in neuronal cultures. Biochem Pharmacol 63:21–29

Li Y, Daniel M, Tollefsbol TO (2011) Epigenetic regulation of caloric restriction in aging. BMC Med 9:98

Lin MT, Beal MF (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443:787–795

Liu C, Wu J, Xu K, Cai F, Gu J, Ma L, Chen J (2010) Neuroprotection by baicalein in ischemic brain injury involves PTEN/AKT pathway. J Neurochem 112:1500–1512

Liu M, Xu Y, Han X, Liang C, Yin L, Xu L, Qi Y, Zhao Y, Peng J, Sun C (2014) Potent effects of flavonoid-rich extract from *Rosa laevigata* Michx fruit against hydrogen peroxide-induced damage in PC12 cells via attenuation of oxidative stress, inflammation and apoptosis. Molecules 19:11816–11832

Long J, Gao H, Sun L, Liu J, Zhao-Wilson X (2009) Grape extract protects mitochondria from oxidative damage and improves locomotor dysfunction and extends lifespan in a Drosophila Parkinson's disease model. Rejuvenation Res 12:321–331

Louw A, Joubert E, Visser K (2013) Phytoestrogenic potential of Cyclopia extracts and polyphenols. Planta Med 79:580–590

Macready AL, Kennedy OB, Ellis JA, Williams CM, Spencer JP, Butler LT (2009) Flavonoids and cognitive function: a review of human randomized controlled trial studies and recommendations for future studies. Genes Nutr 4:227–242

Maher P, Akaishi T, Abe K (2006) Flavonoid fisetin promotes ERK-dependent long-term potentiation and enhances memory. Proc Natl Acad Sci USA 103:16568–16573

Mandel S, Youdim MB (2004) Catechin polyphenols: neurodegeneration and neuroprotection in neurodegenerative diseases. Free Radic Biol Med 37:304–317

Mandel S, Weinreb O, Amit T, Youdim MB (2004) Cell signaling pathways in the neuroprotective actions of the green tea polyphenol (−)-epigallocatechin-3-gallate: implications for neurodegenerative diseases. J Neurochem 88:1555–1569

Mandel SA, Avramovich-Tirosh Y, Reznichenko L, Zheng H, Weinreb O, Amit T, Youdim MB (2005) Multifunctional activities of green tea catechins in neuroprotection. Modulation of cell survival genes, iron-dependent oxidative stress and PKC signaling pathway. Neuro-Signals 14:46–60

Mandel S, Amit T, Bar-Am O, Youdim MB (2007) Iron dysregulation in Alzheimer's disease: multimodal brain permeable iron chelating drugs, possessing neuroprotective-neurorescue and amyloid precursor protein-processing regulatory activities as therapeutic agents. Prog Neurobiol 82:348–360

Margina D, Ilie M, Gradinaru D, Androutsopoulos VP, Kouretas D, Tsatsakis AM (2015) Natural products-friends or foes? Toxicol Lett 236:154–167

Martin SL, Hardy TM, Tollefsbol TO (2013) Medicinal chemistry of the epigenetic diet and caloric restriction. Curr Med Chem 20:4050–4059

Matsuoka Y, Hasegawa H, Okuda S, Muraki T, Uruno T, Kubota K (1995) Ameliorative effects of tea catechins on active oxygen-related nerve cell injuries. J Pharmacol Exp Ther 274:602–608

Mattson MP, Cheng A (2006) Neurohormetic phytochemicals: low-dose toxins that induce adaptive neuronal stress responses. Trends Neurosci 29:632–639

McCann SE, Freudenheim JL, Marshall JR, Graham S (2003) Risk of human ovarian cancer is related to dietary intake of selected nutrients, phytochemicals and food groups. J Nutr 133:1937–1942

McKay DL, Blumberg JB (2002) The role of tea in human health: an update. J Am Coll Nutr 21:1–13

Medina JH, Viola H, Wolfman C, Marder M, Wasowski C, Calvo D, Paladini AC (1998) Neuroactive flavonoids: new ligands for the benzodiazepine receptors. Phytomedicine 5:235–243

Meeran SM, Ahmed A, Tollefsbol TO (2010) Epigenetic targets of bioactive dietary components for cancer prevention and therapy. Clin Epigenetics 1:101–116

Menendez JA, Joven J, Aragones G, Barrajon-Catalan E, Beltran-Debon R, Borras-Linares I, Camps J, Corominas-Faja B, Cufi S, Fernandez-Arroyo S, Garcia-Heredia A, Hernandez-Aguilera A, Herranz-Lopez M, Jimenez-Sanchez C, Lopez-Bonet E, Lozano-Sanchez J, Luciano-Mateo F, Martin-Castillo B, Martin-Paredero V, Perez-Sanchez A, Oliveras-Ferraros C, Riera-Borrull M, Rodriguez-Gallego E, Quirantes-Pine R, Rull A, Tomas-Menor L, Vazquez-Martin A, Alonso-Villaverde C, Micol V, Segura-Carretero A (2013) Xenohormetic and anti-aging activity of secoiridoid polyphenols present in extra virgin olive oil: a new family of gerosuppressant agents. Cell Cycle 12:555–578

Milbury PE, Kalt W (2010) Xenobiotic metabolism and berry flavonoid transport across the blood-brain barrier. J Agric Food Chem 58:3950–3956

Milenkovic D, Deval C, Gouranton E, Landrier JF, Scalbert A, Morand C, Mazur A (2012) Modulation of miRNA expression by dietary polyphenols in apoE deficient mice: a new mechanism of the action of polyphenols. PLoS One 7:e29837

Miller PE, Snyder DC (2012) Phytochemicals and cancer risk: a review of the epidemiological evidence. Nutr Clin Pract 27:599–612

Moderno PM, Carvalho M, Silva BM (2009) Recent patents on *Camellia sinensis*: source of health promoting compounds. Recent Pat Food Nutr Agric 1:182–192

Monagas M, Urpi-Sarda M, Sanchez-Patan F, Llorach R, Garrido I, Gomez-Cordoves C, Andres-Lacueva C, Bartolome B (2010) Insights into the metabolism and microbial biotransformation of dietary flavan-3-ols and the bioactivity of their metabolites. Food Funct 1:233–253

Morley JE (2002) The SAMP8 mouse: a model of Alzheimer disease? Biogerontology 3:57–60

Morselli E, Maiuri MC, Markaki M, Megalou E, Pasparaki A, Palikaras K, Criollo A, Galluzzi L, Malik SA, Vitale I, Michaud M, Madeo F, Tavernarakis N, Kroemer G (2010) The life span-prolonging effect of sirtuin-1 is mediated by autophagy. Autophagy 6:186–188

Morselli E, Marino G, Bennetzen MV, Eisenberg T, Megalou E, Schroeder S, Cabrera S, Benit P, Rustin P, Criollo A, Kepp O, Galluzzi L, Shen S, Malik SA, Maiuri MC, Horio Y, Lopez-Otin C, Andersen JS, Tavernarakis N, Madeo F, Kroemer G (2011) Spermidine and resveratrol induce autophagy by distinct pathways converging on the acetylproteome. J Cell Biol 192:615–629

Murakami A (2014) Dose-dependent functionality and toxicity of green tea polyphenols in experimental rodents. Arch Biochem Biophys 557:3–10

Mylonas C, Kouretas D (1999) Lipid peroxidation and tissue damage. In Vivo (Athens, Greece) 13:295–309

Nakagawa H, Hasumi K, Woo JT, Nagai K, Wachi M (2004) Generation of hydrogen peroxide primarily contributes to the induction of Fe(II)-dependent apoptosis in Jurkat cells by (−)-epigallocatechin gallate. Carcinogenesis 25:1567–1574

Nakao M, Takio S, Ono K (1998) Alkyl peroxyl radical-scavenging activity of catechins. Phytochemistry 49:2379–2382

Nanjo F, Goto K, Seto R, Suzuki M, Sakai M, Hara Y (1996) Scavenging effects of tea catechins and their derivatives on 1,1-diphenyl-2-picrylhydrazyl radical. Free Radic Biol Med 21:895–902

Napoli E, Taroni F, Cortopassi GA (2006) Frataxin, iron-sulfur clusters, heme, ROS, and aging. Antioxid Redox Signal 8:506–516

Neely MD, Montine TJ (2002) CSF lipoproteins and Alzheimer's disease. J Nutr Health Aging 6:383–391

Nifli AP, Bosson-Kouame A, Papadopoulou N, Kogia C, Kampa M, Castagnino C, Stournaras C, Vercauteren J, Castanas E (2005) Monomeric and oligomeric flavanols are agonists of membrane androgen receptors. Exp Cell Res 309:329–339

Nunes AR, Alves MG, Moreira PI, Oliveira PF, Silva BM (2014) Can tea consumption be a safe and effective therapy against diabetes mellitus-induced neurodegeneration? Curr Neuropharmacol 12:475–489

Nunes AR, Alves MG, Tomas GD, Conde VR, Cristovao AC, Moreira PI, Oliveira PF, Silva BM (2015) Daily consumption of white tea (*Camellia sinensis* (L.)) improves the cerebral cortex metabolic and oxidative profile in prediabetic Wistar rats. Br J Nutr 113:832–842

Nurk E, Refsum H, Drevon CA, Tell GS, Nygaard HA, Engedal K, Smith AD (2009) Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance. J Nutr 139:120–127

Obrenovich ME, Nair NG, Beyaz A, Aliev G, Reddy VP (2010) The role of polyphenolic antioxidants in health, disease, and aging. Rejuvenation Res 13:631–643

Obrenovich ME, Li Y, Parvathaneni K, Yendluri BB, Palacios HH, Leszek J, Aliev G (2011) Antioxidants in health, disease and aging. CNS Neurol Disord Drug Targets 10:192–207

Okello EJ, McDougall GJ, Kumar S, Seal CJ (2011) In vitro protective effects of colon-available extract of *Camellia sinensis* (tea) against hydrogen peroxide and beta-amyloid (Abeta((1-42))) induced cytotoxicity in differentiated PC12 cells. Phytomedicine 18:691–696

Ovaskainen ML, Torronen R, Koponen JM, Sinkko H, Hellstrom J, Reinivuo H, Mattila P (2008) Dietary intake and major food sources of polyphenols in Finnish adults. J Nutr 138:562–566

Pallauf K, Rimbach G (2013) Autophagy, polyphenols and healthy ageing. Ageing Res Rev 12:237–252

Pannala AS, Rice-Evans CA, Halliwell B, Singh S (1997) Inhibition of peroxynitrite-mediated tyrosine nitration by catechin polyphenols. Biochem Biophys Res Commun 232:164–168

Papandreou MA, Dimakopoulou A, Linardaki ZI, Cordopatis P, Klimis-Zacas D, Margarity M, Lamari FN (2009) Effect of a polyphenol-rich wild blueberry extract on cognitive performance of mice, brain antioxidant markers and acetylcholinesterase activity. Behav Brain Res 198:352–358

Paris D, Mathura V, Ait-Ghezala G, Beaulieu-Abdelahad D, Patel N, Bachmeier C, Mullan M (2011) Flavonoids lower Alzheimer's Abeta production via an NFkappaB dependent mechanism. Bioinformation 6:229–236

Patir H, Sarada SK, Singh S, Mathew T, Singh B, Bansal A (2012) Quercetin as a prophylactic measure against high altitude cerebral edema. Free Radic Biol Med 53:659–668

Perez-De La Cruz V, Elinos-Calderon D, Robledo-Arratia Y, Medina-Campos ON, Pedraza-Chaverri J, Ali SF, Santamaria A (2009) Targeting oxidative/nitrergic stress ameliorates motor impairment, and attenuates synaptic mitochondrial dysfunction and lipid peroxidation in two models of Huntington's disease. Behav Brain Res 199:210–217

Perez-Jimenez J, Neveu V, Vos F, Scalbert A (2010) Identification of the 100 richest dietary sources of polyphenols: an application of the phenol-explorer database. Eur J Clin Nutr 64(Suppl 3):S112–S120

Perry G, Cash AD, Smith MA (2002) Alzheimer disease and oxidative stress. J Biomed Biotechnol 2:120–123

Pitchumoni SS, Doraiswamy PM (1998) Current status of antioxidant therapy for Alzheimer's disease. J Am Geriatr Soc 46:1566–1572

Potenza MA, Marasciulo FL, Tarquinio M, Tiravanti E, Colantuono G, Federici A, Kim JA, Quon MJ, Montagnani M (2007) EGCG, a green tea polyphenol, improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial I/R injury in SHR. Am J Physiol Endocrinol Metab 292:E1378–E1387

Prochazkova D, Bousova I, Wilhelmova N (2011) Antioxidant and prooxidant properties of flavonoids. Fitoterapia 82:513–523

Przedborski S, Vila M, Jackson-Lewis V (2003) Neurodegeneration: what is it and where are we? J Clin Investig 111:3–10

Rahman I, Biswas SK, Kirkham PA (2006) Regulation of inflammation and redox signaling by dietary polyphenols. Biochem Pharmacol 72:1439–1452

Rambold AS, Miesbauer M, Olschewski D, Seidel R, Riemer C, Smale L, Brumm L, Levy M, Gazit E, Oesterhelt D, Baier M, Becker CF, Engelhard M, Winklhofer KF, Tatzelt J (2008) Green tea extracts interfere with the stress-protective activity of PrP and the formation of PrP. J Neurochem 107:218–229

Recchia A, Debetto P, Negro A, Guidolin D, Skaper SD, Giusti P (2004) Alpha-synuclein and Parkinson's disease. FASEB J 18:617–626

Reed TT (2011) Lipid peroxidation and neurodegenerative disease. Free Radic Biol Med 51:1302–1319

Reed T, Perluigi M, Sultana R, Pierce WM, Klein JB, Turner DM, Coccia R, Markesbery WR, Butterfield DA (2008) Redox proteomic identification of 4-hydroxy-2-nonenal-modified brain proteins in amnestic mild cognitive impairment: insight into the role of lipid peroxidation in the progression and pathogenesis of Alzheimer's disease. Neurobiol Dis 30:107–120

Reiners JJ Jr, Lee JY, Clift RE, Dudley DT, Myrand SP (1998) PD98059 is an equipotent antagonist of the aryl hydrocarbon receptor and inhibitor of mitogen-activated protein kinase kinase. Mol Pharmacol 53:438–445

Reiter RJ (1995) Oxidative processes and antioxidative defense mechanisms in the aging brain. FASEB J 9:526–533

Remely M, Lovrecic L, de la Garza AL, Migliore L, Peterlin B, Milagro FI, Martinez AJ, Haslberger AG (2015) Therapeutic perspectives of epigenetically active nutrients. Br J Pharmacol 172:2756–2768

Ren J, Fan C, Chen N, Huang J, Yang Q (2011) Resveratrol pretreatment attenuates cerebral ischemic injury by upregulating expression of transcription factor Nrf2 and HO-1 in rats. Neurochem Res 36:2352–2362

Rezai-Zadeh K, Shytle D, Sun N, Mori T, Hou H, Jeanniton D, Ehrhart J, Townsend K, Zeng J, Morgan D, Hardy J, Town T, Tan J (2005) Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice. J Neurosci 25:8807–8814

Rice-Evans C (1999) Implications of the mechanisms of action of tea polyphenols as antioxidants in vitro for chemoprevention in humans. Proc Soc Exp Biol Med Soc Exp Biol Med 220:262–266

Rice-Evans CA, Miller NJ, Bolwell PG, Bramley PM, Pridham JB (1995) The relative antioxidant activities of plant-derived polyphenolic flavonoids. Free Radic Res 22:375–383

Rice-Evans C, Miller N, Paganga G (1997) Antioxidant properties of phenolic compounds. Trends Plant Sci 2:152–159
Richa Tyagi EM, Meeta M, Ruhal D (2015) The phisiochemical standards of *Dyerophytum Rubrum* Gibs. EX WT and *Plumbago Zeylanica* L leaf: a co-comparison. World J Pharm Pharm Sci 4:6
Riederer P, Sofic E, Rausch WD, Schmidt B, Reynolds GP, Jellinger K, Youdim MB (1989) Transition metals, ferritin, glutathione, and ascorbic acid in Parkinsonian brains. J Neurochem 52:515–520
Rigacci S, Stefani M (2015) Nutraceuticals and amyloid neurodegenerative diseases: a focus on natural phenols. Expert Rev Neurother 15:41–52
Roche A, Ross E, Walsh N, O'Donnell K, Williams A, Klapp M, Fullard N, Edelstein S (2015) Representative literature on the phytonutrients category: phenolic acids. Crit Rev Food Sci Nutr. doi:10.1080/10408398.2013.865589
Rossi L, Mazzitelli S, Arciello M, Capo CR, Rotilio G (2008) Benefits from dietary polyphenols for brain aging and Alzheimer's disease. Neurochem Res 33:2390–2400
Russo A, Acquaviva R, Campisi A, Sorrenti V, Di Giacomo C, Virgata G, Barcellona ML, Vanella A (2000) Bioflavonoids as antiradicals, antioxidants and DNA cleavage protectors. Cell Biol Toxicol 16:91–98
Ryan J, Croft K, Mori T, Wesnes K, Spong J, Downey L, Kure C, Lloyd J, Stough C (2008) An examination of the effects of the antioxidant Pycnogenol on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population. J Psychopharmacol 22:553–562
Salah N, Miller NJ, Paganga G, Tijburg L, Bolwell GP, Rice-Evans C (1995) Polyphenolic flavanols as scavengers of aqueous phase radicals and as chain-breaking antioxidants. Arch Biochem Biophys 322:339–346
Sandoval-Acuna C, Ferreira J, Speisky H (2014) Polyphenols and mitochondria: an update on their increasingly emerging ROS-scavenging independent actions. Arch Biochem Biophys 559:75–90
Scalbert A, Johnson IT, Saltmarsh M (2005) Polyphenols: antioxidants and beyond. Am J Clin Nutr 81:215s–217s
Schaffer S, Halliwell B (2012) Do polyphenols enter the brain and does it matter? Some theoretical and practical considerations. Genes Nutr 7:99–109
Schaffer S, Eckert GP, Schmitt-Schillig S, Muller WE (2006) Plant foods and brain aging: a critical appraisal. Forum Nutr 59:86–115
Schaffer S, Asseburg H, Kuntz S, Muller WE, Eckert GP (2012) Effects of polyphenols on brain ageing and Alzheimer's disease: focus on mitochondria. Mol Neurobiol 46:161–178
Schroeter H, Spencer JP, Rice-Evans C, Williams RJ (2001) Flavonoids protect neurons from oxidized low-density-lipoprotein-induced apoptosis involving c-Jun N-terminal kinase (JNK), c-Jun and caspase-3. Biochem J 358:547–557
Schroeter H, Bahia P, Spencer JP, Sheppard O, Rattray M, Cadenas E, Rice-Evans C, Williams RJ (2007) (−)Epicatechin stimulates ERK-dependent cyclic AMP response element activity and up-regulates GluR2 in cortical neurons. J Neurochem 101: 1596–1606
Sears B, Ricordi C (2012) Role of fatty acids and polyphenols in inflammatory gene transcription and their impact on obesity, metabolic syndrome and diabetes. Eur Rev Med Pharmacol Sci 16:1137–1154
Seeram NP, Henning SM, Niu Y, Lee R, Scheuller HS, Heber D (2006) Catechin and caffeine content of green tea dietary supplements and correlation with antioxidant capacity. J Agric Food Chem 54:1599–1603
Shah ZA, Li RC, Ahmad AS, Kensler TW, Yamamoto M, Biswal S, Dore S (2010) The flavanol (−)-epicatechin prevents stroke damage through the Nrf2/HO1 pathway. J Cereb Blood Flow Metab 30:1951–1961
Shanafelt TD, Call TG, Zent CS, LaPlant B, Bowen DA, Roos M, Secreto CR, Ghosh AK, Kabat BF, Lee MJ, Yang CS, Jelinek DF, Erlichman C, Kay NE (2009) Phase I trial of daily oral polyphenon E in patients with asymptomatic Rai stage 0 to II chronic lymphocytic leukemia. J Clin Oncol 27:3808–3814
Shin BY, Jin SH, Cho IJ, Ki SH (2012) Nrf2-ARE pathway regulates induction of Sestrin-2 expression. Free Radic Biol Med 53:834–841
Si H, Liu D (2014) Dietary antiaging phytochemicals and mechanisms associated with prolonged survival. J Nutr Biochem 25:581–591
Simao F, Matte A, Pagnussat AS, Netto CA, Salbego CG (2012) Resveratrol prevents CA1 neurons against ischemic injury by parallel modulation of both GSK-3beta and CREB through PI3-K/Akt pathways. Eur J Neurosci 36:2899–2905
Simonyi A, Wang Q, Miller RL, Yusof M, Shelat PB, Sun AY, Sun GY (2005) Polyphenols in cerebral ischemia: novel targets for neuroprotection. Mol Neurobiol 31:135–147
Singer C (2012) Managing the patient with newly diagnosed Parkinson disease. Clevel Clin J Med 79(Suppl 2):S3–S7
Singletary K, Milner J (2008) Diet, autophagy, and cancer: a review. Cancer Epidemiol Biomark Prev 17:1596–1610
Smith C, Mitchinson MJ, Aruoma OI, Halliwell B (1992) Stimulation of lipid peroxidation and hydroxyl-radical generation by the contents of human atherosclerotic lesions. Biochem J 286(Pt 3):901–905
Smith RA, Hartley RC, Cocheme HM, Murphy MP (2012) Mitochondrial pharmacology. Trends Pharmacol Sci 33:341–352
Somani SJ, Modi KP, Majumdar AS, Sadarani BN (2015) Phytochemicals and their potential usefulness in inflammatory bowel disease. Phytother Res 29:339–350
Spanou CI, Veskoukis AS, Stagos D, Liadaki K, Aligiannis N, Angelis A, Skaltsounis AL, Anastasiadi M, Haroutounian SA, Kouretas D (2012) Effects of Greek legume plant extracts on xanthine oxidase, catalase and superoxide dismutase activities. J Physiol Biochem 68:37–45
Spencer JP (2008) Flavonoids: modulators of brain function? Br J Nutr 99(E Suppl 1):Es60–Es77
Spencer JP (2009) Flavonoids and brain health: multiple effects underpinned by common mechanisms. Genes Nutr 4:243–250
Spencer JP, Schroeter H, Crossthwaithe AJ, Kuhnle G, Williams RJ, Rice-Evans C (2001) Contrasting influences of glucuronidation and O-methylation of epicatechin on hydrogen peroxide-induced cell death in neurons and fibroblasts. Free Radic Biol Med 31:1139–1146
Sramek JJ, Cutler NR (1999) Recent developments in the drug treatment of Alzheimer's disease. Drugs Aging 14:359–373
Stagos D, Portesis N, Spanou C, Mossialos D, Aligiannis N, Chaita E, Panagoulis C, Reri E, Skaltsounis L, Tsatsakis AM, Kouretas D (2012) Correlation of total polyphenolic content with antioxidant and antibacterial activity of 24 extracts from Greek domestic Lamiaceae species. Food Chem Toxicol 50:4115–4124
Stefani M, Rigacci S (2014) Beneficial properties of natural phenols: highlight on protection against pathological conditions associated with amyloid aggregation. BioFactors 40:482–493
St-Pierre J, Buckingham JA, Roebuck SJ, Brand MD (2002) Topology of superoxide production from different sites in the mitochondrial electron transport chain. J Biol Chem 277:44784–44790
Subczynski WK, Hyde JS (1983) Concentration of oxygen in lipid bilayers using a spin-label method. Biophys J 41:283–286
Tahara S (2007) A journey of twenty-five years through the ecological biochemistry of flavonoids. Biosci Biotechnol Biochem 71:1387–1404

Talavera S, Felgines C, Texier O, Besson C, Gil-Izquierdo A, Lamaison JL, Remesy C (2005) Anthocyanin metabolism in rats and their distribution to digestive area, kidney, and brain. J Agric Food Chem 53:3902–3908

Tang S, Kerry JP, Sheehan D, Buckley DJ, Morrissey PA (2001) Antioxidative effect of added tea catechins on susceptibility of cooked red meat, poultry and fish patties to lipid oxidation. Food Res Int 34:651–657

Thanan R, Oikawa S, Hiraku Y, Ohnishi S, Ma N, Pinlaor S, Yongvanit P, Kawanishi S, Murata M (2015) Oxidative stress and its significant roles in neurodegenerative diseases and cancer. Int J Mol Sci 16:193–217

Tsang AH, Chung KK (2009) Oxidative and nitrosative stress in Parkinson's disease. Biochim Biophys Acta 1792:643–650

Uddin SN, Akond M, Mubassara S, Yesmin MN (2008) Antioxidant and antibacterial activities of Trema cannabina Middle-East. J Sci Res 3:105–108

Valerio A, Boroni F, Benarese M, Sarnico I, Ghisi V, Bresciani LG, Ferrario M, Borsani G, Spano P, Pizzi M (2006) NF-kappaB pathway: a target for preventing beta-amyloid (Abeta)-induced neuronal damage and Abeta42 production. Eur J Neurosci 23:1711–1720

Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39:44–84

Van Amelsvoort JM, Van Hof KH, Mathot JN, Mulder TP, Wiersma A, Tijburg LB (2001) Plasma concentrations of individual tea catechins after a single oral dose in humans. Xenobiotica 31:891–901

Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, Bloch DA, Nelson LM (2003) Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol 157:1015–1022

Vasanthi HR, ShriShriMal N, Das DK (2012) Phytochemicals from plants to combat cardiovascular disease. Curr Med Chem 19:2242–2251

Visioli F, Bellomo G, Galli C (1998) Free radical-scavenging properties of olive oil polyphenols. Biochem Biophys Res Commun 247:60–64

Visioli F, De La Lastra CA, Andres-Lacueva C, Aviram M, Calhau C, Cassano A, D'Archivio M, Faria A, Fave G, Fogliano V, Llorach R, Vitaglione P, Zoratti M, Edeas M (2011) Polyphenols and human health: a prospectus. Crit Rev Food Sci Nutr 51:524–546

Vitrac X, Desmouliere A, Brouillaud B, Krisa S, Deffieux G, Barthe N, Rosenbaum J, Merillon JM (2003) Distribution of [14C]-trans-resveratrol, a cancer chemopreventive polyphenol, in mouse tissues after oral administration. Life Sci 72:2219–2233

Wheeler DS, Wheeler WJ (2004) The medicinal chemistry of tea. Drug Dev Res 61:45–65

Wightman EL, Haskell CF, Forster JS, Veasey RC, Kennedy DO (2012) Epigallocatechin gallate, cerebral blood flow parameters, cognitive performance and mood in healthy humans: a double-blind, placebo-controlled, crossover investigation. Hum Psychopharmacol 27:177–186

Williams RJ, Spencer JP (2012) Flavonoids, cognition, and dementia: actions, mechanisms, and potential therapeutic utility for Alzheimer disease. Free Radic Biol Med 52:35–45

Wimo A, Winblad B, Aguero-Torres H, von Strauss E (2003) The magnitude of dementia occurrence in the world. Alzheimer Dis Assoc Disord 17:63–67

Wink M (2003) Evolution of secondary metabolites from an ecological and molecular phylogenetic perspective. Phytochemistry 64:3–19

Winner B, Kohl Z, Gage FH (2011) Neurodegenerative disease and adult neurogenesis. Eur J Neurosci 33:1139–1151

Wu Z, Song L, Liu SQ, Huang D (2014) Tanshinones extend chronological lifespan in budding yeast *Saccharomyces cerevisiae*. Appl Microbiol Biotechnol 98:8617–8628

Xu YW, Sun L, Liang H, Sun GM, Cheng Y (2010) 12/15-Lipoxygenase inhibitor baicalein suppresses PPAR gamma expression and nuclear translocation induced by cerebral ischemia/reperfusion. Brain Res 1307:149–157

Xue X, Qu XJ, Yang Y, Sheng XH, Cheng F, Jiang EN, Wang JH, Bu W, Liu ZP (2010) Baicalin attenuates focal cerebral ischemic reperfusion injury through inhibition of nuclear factor kappaB p65 activation. Biochem Biophys Res Commun 403:398–404

Yang CS, Hong J, Hou Z, Sang S (2004) Green tea polyphenols: antioxidative and prooxidative effects. J Nutr 134:3181s

Youdim KA, Joseph JA (2001) A possible emerging role of phytochemicals in improving age-related neurological dysfunctions: a multiplicity of effects. Free Radic Biol Med 30:583–594

Youdim KA, Dobbie MS, Kuhnle G, Proteggente AR, Abbott NJ, Rice-Evans C (2003) Interaction between flavonoids and the blood-brain barrier: in vitro studies. J Neurochem 85:180–192

Youdim KA, Qaiser MZ, Begley DJ, Rice-Evans CA, Abbott NJ (2004a) Flavonoid permeability across an in situ model of the blood-brain barrier. Free Radic Biol Med 36:592–604

Youdim KA, Shukitt-Hale B, Joseph JA (2004b) Flavonoids and the brain: interactions at the blood-brain barrier and their physiological effects on the central nervous system. Free Radic Biol Med 37:1683–1693

Yun JW (2010) Possible anti-obesity therapeutics from nature—a review. Phytochemistry 71:1625–1641

Zamora-Ros R, Andres-Lacueva C, Lamuela-Raventós RM, Berenguer T, Jakszyn P, Barricarte A, Ardanaz E, Amiano P, Dorronsoro M, Larrañaga N (2010) Estimation of dietary sources and flavonoid intake in a Spanish adult population (EPIC-Spain). J Am Diet Assoc 110:390–398

Zhang W, Potrovita I, Tarabin V, Herrmann O, Beer V, Weih F, Schneider A, Schwaninger M (2005) Neuronal activation of NF-kappaB contributes to cell death in cerebral ischemia. J Cereb Blood Flow Metab 25:30–40