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Botanical phenolics and brain health

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Abstract

The high demand for molecular oxygen, the enrichment of polyunsaturated fatty acids in membrane phospholipids and the relatively low abundance of antioxidant defense enzymes are factors rendering cells in the central nervous system (CNS) particularly vulnerable to oxidative stress. Excess production of reactive oxygen species (ROS) in the brain has been implicated as a common underlying factor for the etiology of a number of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and stroke. While ROS are generated by enzymatic and non-enzymatic reactions in the mitochondria and cytoplasm under normal conditions, excessive production under pathological conditions is associated with activation of Ca^{2+}-dependent enzymes including proteases, phospholipases, nucleases, and alterations of signaling pathways which subsequently lead to mitochondrial dysfunction, release of inflammatory factors and apoptosis. In recent years, there is considerable interest to investigate anti-oxidative and anti-inflammatory effects of phenolic compounds from different botanical sources. In this review, we describe oxidative mechanisms associated with AD, PD, and stroke, and evaluate neuroprotective effects of phenolic compounds, such as resveratrol from grape and red wine, curcumin from turmeric, apocynin from *Picrorhiza kurroa,* and epi-gallocatechin from green tea. The main goal is to provide a better understanding of the mode of action of these compounds and assess their use as therapeutics to ameliorate age-related neurodegenerative diseases.

2. Introduction

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as superoxide anion, hydroxyl radicals, hydrogen peroxide, lipid peroxyl radicals, nitric oxide, and peroxynitrite, are generated in different cellular systems through enzymatic and non-enzymatic reactions (Sun & Chen 1998). Many pathological conditions are associated with excessive production of ROS/RNS which can attack key proteins, lipids and DNA, alter signal transduction pathways, destroy membranes and subcellular organelles, and subsequently result in apoptosis and cell death. In the presence of transition metals or redox cycling compounds (including quinones), reactive oxygen species such as superoxide can be converted to the more reactive hydroxy radicals. In some cellular conditions, superoxide anions and nitric oxide can react with each other and form peroxynitrite, a highly toxic anionic compound.

A number of intracellular enzymes are known to produce ROS/RNS, e.g., xanthine/xanthine oxidase, NADPH oxidase, cytochrome P450, nitric oxide synthases, prostaglandin synthases, and enzymes in the electron transport chain in mitochondria. In the cellular/subcellular systems, however, production of ROS/RNS through these oxidative enzymes can be counteracted by

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intracellular antioxidants, including glutathione, vitamin C and E, Coenzyme Q, and by antioxidant enzymes such as superoxide dismutases (SOD), catalase, and glutathione peroxidase. Recent studies also recognize the role of protein kinases and signaling molecules in regulating transcription factors, such as NFκB and Nrf-2/ARE, and thus genes involved in inflammation and oxidant responses (Lim *et al.* 2007a, Mattson 2008).

The high demand for molecular oxygen, the high levels of polyunsaturated fatty acids in neural membrane phospholipids, and the high iron content are important factors rendering cells in the central nervous system (CNS) to oxidative stress. Oxidative stress is an important underlying factor for a number of neurodegenerative disesaes (Halliwell 2006). Neurons are particularly at risk to oxidative stress because many major antioxidant defence mechanisms, such as GSH, Nrf-2, and metallothienin, seem to be localized to astrocytes. Excessive ROS production is associated with activation of the Ca^{2+}-dependent enzymes including proteases, phospholipases, and nucleases and alterations of signaling pathways that lead to mitochondrial dysfunction and neuronal apoptosis (Mattson 2007). Increase in oxidative products, such as 4-hydroxynonenal (HNE) for lipid peroxidation, 3-nitrotyrosine (3-NT) for protein carbonyl and protein nitrotyrosine adducts, and 8-hydroxy-deoxyguanosine (8-OHdG) for DNA damage, associated with neurodegenerative diseases support the notion that oxidative stress is a common element in the progression of these diseases (Halliwell 2006, Simonian & Coyle 1996, Sun & Chen 1998).

Oxidative stress is also a significant factor associated with the decline of function in the aging brain. With the disproportional increase in aging population (baby boomers) in the next decade, there is increasing attention to develop nutritional therapies to combat these age-related oxidative processes. Considerable attention is focused on botanicals in vegetables, fruits, grains, roots, flowers, seeds, tea and red wine. Other nutritional interventions such as dietary restriction and a Mediterranean diet have also captured considerable attention, in particular among older population and subjects with mild cognitive impairments (Burgener *et al.* 2008). Compounds such as resveratrol from grape and wine, curcumin from turmeric, and epigallocatechin from green tea, are becoming recognized for their protective effects against inflammatory diseases, cancers, cardiovascular and neurodegenerative diseases. Although the mechanisms whereby these compounds display beneficial effects remain elusive, there is increasing evidence to support their anti-oxidative, anti-inflammatory, anti-apoptotic and metal-chelating properties (Rice-Evans & Miller 1997, Ndiaye *et al.* 2005). Besides these polyphenolic compounds, there is increasing evidence for NADPH oxidase as an important source of ROS in the central nervous system. Recent studies also place emphasis on ability for apocynin, a phenolic compound derived from *Picrorhiza kurroa* to inhibit NADPH oxidase (Fig 1). The major goal for this review is to describe oxidative mechanisms underlying neurodegenerative diseases such as AD, PD and stroke and to assess whether these phenolic compounds may offer neuroprotective effects.

3. Oxidative stress and neurodegenerative disorders

3-a. Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia affecting more than 4 million people in the U.S. and 15 to 20 million worldwide. With the disproportional increase in the aging population in the next decade, these numbers are projected to triple by 2050. Common pathological hallmarks for AD are accumulation of amyloid plaques and neurofibrillary tangles (McKeel *et al.* 2004). Besides genetic factors which comprise around 7% of familial AD patients (FAD), epi-genetic and environmental factors are known to play an important role in the onset of sporadic AD. Cardiovascular abnormalities such as hypertension, diabetes, mini-stroke, and atherosclerosis are factors precipitating the increased risk for AD.

Because increase in oxidative stress is associated with early development of AD (Butterfield *et al.* 2002), there is interest to search for effective therapy to combat the oxidative damage in this disease. There is evidence that at least part of the oxidative mechanism is contributed by the amyloid beta (Abeta) peptides. These peptides (39-43 amino acids) are released from the amyloid precursor protein through beta and gamma secretases and upon release, can be aggregated to oligomeric form. Oligomeric Abeta can confer oxidative insult to neurons and glial cells and initiate changes in synaptic plasticity, events occurring long before their deposition to form the amyloid plaques (Selkoe 2001). Although the mechanism for oligomeric Abeta to confer cytotoxicity that results in synaptic dysfunction is not clearly understood, there is evidence that these peptides can confer specific action on the N-methyl-D-aspartic acid (NMDA) receptors (Snyder *et al.* 2005). Aside from regulating synaptic plasticity and memory function, activation of NMDA receptor is coupled to ROS production (Kishida & Klann 2007, Kishida *et al.* 2005). Recent studies further demonstrate that Abeta can induce ROS production in neurons through an NMDA receptor-dependent process (De Felice *et al.* 2007, Shelat *et al.* 2008). Thus, NADPH oxidase may be common in NMDA- and Abeta-induced ROS production, and activation of signaling pathways, including PKC and MAPK, which in turn, lead to activation of cytosolic phospholipase A2 ($cPLA_2$) and release of arachidonic acid (AA) (Shelat et al. 2008). Arachidonic acid not only is a precursor for synthesis of prostaglandins, but is also known to serve as a retrograde transmitter in regulating synaptic plasticity (Sang & Chen 2006). Studies by Kriem et al (2005) demonstrated the involvement of $cPLA_2$ in Abeta-induced apoptosis in neurons (Kriem *et al.* 2005).

Intracellular Abeta may target cytoplasmic signaling pathways and impair mitochondrial function (Wang *et al.* 2007b). In astrocytes, Abeta treatment was shown to cause the decrease in mitochondrial membrane potential, and this was partly due to activation of phospholipase A2 (Zhu *et al.* 2006). In most instances, mitochondrial dysfunction is associated with increase production of ROS, release of cytochrome C, which in turn, triggers the apoptotic pathways. Abeta-mediated ROS production is also linked to increased inflammatory responses, including increased production of cytokines, nitric oxide and eicosanoids (Mancuso *et al.* 2007, Butterfield et al. 2002, Akama & Van Eldik 2000). Other contributions from astrocytes include alterations in the synthesis of ApoE (major risk factor for AD) and D-serine, which is an endogenous activator of NMDA receptors.

NADPH oxidase has been regarded an important source of ROS that mediate the inflammatory responses in astrocytes and microglial cells in the brain. In fact, Abeta-induced ROS from NADPH oxidase in astrocytes is a key factor in mediating neuronal death (Abramov *et al.* 2004). Therefore, there is strong rationale to develop antioxidant strategy to ameliorate the inflammatory responses associated with the progression of AD. Many recent studies have provided compelling evidence to support dietary supplement of polyphenolic compounds from plant sources to minimize the oxidative events in the AD brain (Anekonda 2006, Chauhan & Sandoval 2007, Ringman *et al.* 2005). These herbal alternatives may provide greater therapeutic benefit compared to a single-ingredient synthetic pharmaceutical drug which normally has serious side effects (Kotilinek *et al.* 2008). Table 1 (top) provides a summary of recent studies testing different botanicals on AD models.

3-b. Parkinson's disease

Parkinson's disease (PD) affects approximately 1% of the population over the age of 50. The clinical manifestations of PD include tremors, bradykinesia, muscle rigidity, and akinesia. The pathological landmarks include a progressive loss of dopaminergic neurons in the substantia nigra (Cardoso *et al.* 2005). Despite numerous hypotheses and speculations for the etiology of PD, oxidative stress remains the strongest leading theory (Miller *et al.* 2008).

Increased risk for PD is correlated with exposure to environmental factors including heavy metals and herbicides (Brooks *et al.* 1999, Liou *et al.* 1997, Yang & Sun 1998b). MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is an environmental toxin which can selectively damage the substantia nigra and produces Parkinson-like symptoms in animal models and in humans. Studies with this PD model have provided important information about the possible cause of PD (Adams & Odunze 1991, Langston *et al.* 1987, Schapira 1996). Besides MPTP, other environmental toxins including rotenone, manganese (Sun *et al.* 1993), dimethoxyphenylethylamine (DMPEA) (Koshimura *et al.* 1997) and paraquat (Li & Sun 1999, Yang & Sun 1998a, Yang & Sun 1998b) also target dopamine neurons. These agents can make their way to the substantia nigra and induce apoptotic pathways in dopaminergic neurons (Schober 2004, Lim *et al.* 2007b).

Dopamine is a neurotransmitter that can undergo metabolism either by monoamine oxidase (MAO) or by autooxidation, producing H_2O_2, superoxide anion, and hydroxyl radicals. In addition, nitric oxide, which is produced through inflammation-induced microglia activation or excitotoxic insults (Abekawa *et al.* 1997, Gonzalez-Hernandez *et al.* 1996), may also play a role in the pathogenesis of PD. Formation of peroxynitrite anions through the combination of ROS with nitric oxide may confer additional toxicity to dopaminergic neurons.

Microglia activation is an important factor contributing to the inflammatory responses in PD (Castano *et al.* 1998, Gao *et al.* 2003b). Earlier studies demonstrated higher levels of microglia in the PD brain as compared to the age-matched control brain (McGeer *et al.* 1988). Activated microglia are present in the substantia nigra in several models of PD, including those induced by exposure to MPTP, rotenone, and 6-OHDA (Block *et al.* 2006, Gao *et al.* 2002). Abnormal accumulation of iron in microglia and increased levels of α-synuclein are important pathological features in these models. The ability for microglia to produce high levels of ROS through NADPH oxidase is regarded as an important factor underlying the MPTP-induced dopaminergic neurodegeneration (Gao *et al.* 2003a, Gao et al. 2003b, Mander *et al.* 2006, Wu *et al.* 2003). In our recent study with BV2 microglial cells, paraquat-induced ROS through NADPH oxidase was shown to require protein kinases such as PKCdelta and ERK1/2 (Miller *et al.* 2007). In microglia-neuron coculture, microglia lacking functional NADPH oxidase failed to produce neurotoxicity in response to paraquat (Wu *et al.* 2005). The important role of microglia in pathogenesis of PD can be demonstrated by the ability for minocyline, an antibiotic known to inhibit microglial activation to attenuate the neurotoxicity caused by rotenone (Casarejos *et al.* 2006).

A number of studies have demonstrated the protective effects of plant phenolics against brain damage in PD. These studies have used either a single compound such as resveratrol, curcumin, EGCG, or a complex mixture of extracts from grape, blueberry and green tea (Weinreb *et al.* 2004, Mercer *et al.* 2005, Chen *et al.* 2007, Masuda *et al.* 2006). Table 1 provides a summary of the studies using different botanicals on PD models. The neuroprotective effects of these phenolic compounds are attributed in part to the free radical scavenging, iron/metal chelating, and their anti-inflammatory properties. There is evidence that these phenolic compounds can target specific signaling pathways and interact with specific proteins, including aggregation of alpha-synuclein (Masuda et al. 2006, Ramassamy 2006, Vafeiadou *et al.* 2007).

3-c. Stroke

Stroke is the third leading cause of death and the first cause of disability in aging adults. The primary cause of stroke is the interruption of cerebral blood flow either by an arterial or venous obstruction or a cardiac arrest. The pathological manifestations in stroke are diverse, depending on the severity, duration, and localization of the ischemic damage. In the past, many animal models have been developed in which blood flow is focally or globally, permanently or transiently, completely or incompletely interrupted. The most widely established methods of

global cerebral ischemia in rodents (rats, mice or gerbils) are the 2- and 4-vessel occlusion. In gerbils, occlusion of both common carotid arteries (CCA) for 5 min can cause delayed neuronal death (DND) of pyramidal neurons in the hippocampal CA1 area after 4 days (Wang *et al.* 2002). In addition, the DND is accompanied by increased reactive astrocytes and microglial cells in the injured area (Wang et al. 2002).

Focal cerebral ischemia is usually produced by occlusion of the middle cerebral artery (MCA), either through surgical exposure of the artery after craniotomy or by inserting a suture from the CCA to the MCA to block the blood flow (Chan *et al.* 1990). Cessation of cerebral blood flow is accompanied by rapid metabolic changes including decrease in ATP production, neuronal membrane depolarization and release of excitatory neurotransmitters. Despite obvious limitations with each model, the focal ischemic model appears to reflect the most common form of clinical stroke. In focal ischemia followed by reperfusion (I/R), cerebral infarcts with extensive loss of neurons and activation of glial cells are found within 12 to 24 hours after the insult. The penumbral area surrounding the ischemic core is comprised of a large number of reactive astrocytes and microglial cells. Factors causing activation of glial cells in the penumbral area and their role in preventing the spreading of depression and restoring neuronal function remain to be an important area of study.

Oxidative stress has been regarded as a substantial underlying cause of brain damage and neuronal dysfunction after cerebral I/R (Chan 2001). However, the mechanism(s) underlying ROS production and how neurons and glial cells respond to I/R has not been clearly elucidated. Earlier studies with neurons in culture demonstrated the role of ionotropic glutamate receptors, particularly the NMDA subtype, in triggering massive Ca^{2+} influx and in turn, the activation of Ca^{2+}-dependent enzymes that trigger mitochondrial dysfunction and apoptotic cell death (Choi 1992). Although mitochondrial dysfunction is known to produce ROS that causes neuronal apoptosis in cerebral ischemia (Chan 2004), recent studies also provided evidence for the involvement of ROS from NADPH oxidase (Wang *et al.* 2006b, Tang *et al.* 2007). In order to combat the deleterious effects of oxidative stress associated with I/R, a number of studies have attempted to upregulate antioxidant enzymes, e.g., superoxide dismutases, catalase and glutathione peroxidase. Studies with transgenic mice overexpressing SOD1 or GSH-Px-1 have provided support for an important role of these enzymes to remove superoxide and decrease oxidative injury in both global and transient MCAO ischemic models (Saito *et al.* 2005).

The underlying role of oxidative stress in neuronal damage after I/R also raises attention to possible beneficial effects of polyphenolic compounds from different plant sources (Bravo 1998, Deschamps *et al.* 2001, Voko *et al.* 2003, Youdim & Joseph 2001). Studies suggest that some polyphenols can be preventative as well and may thus can act at multiple levels to influence both the early and late phases in the progression of stroke (Curin *et al.* 2006, Simonyi *et al.* 2005). Data in Table 1 provide a summary of recent studies testing different botanicals on stroke models.

4. Botanical phenolics and neurodegenerative disorders

The use of plant-derived supplements for improving health is gaining popularity because most people consider these natural products to be safer and produce less side effects than synthetic drugs (Raskin *et al.* 2002). Today, one in three Americans use herbal supplements; consumption is generally greater among woman, patients undergoing surgery, and elderly men (Ang-Lee *et al.* 2001, Morelli & Naquin 2002). There are more than 50 different plant species and over 8000 phenolic compounds identified either in single, pure molecular form or in specific proportions of differing plant extracts. Investigating the health benefits of these natural compounds is an enormous challenge to modern medicine.

Polyphenols such as resveratrol were initially identified as the plant's defensive response against stress from ultraviolet radiation, pathogens, and physical damage (Ferguson 2001). For this and other reasons, the polyphenol content in a specific plant source may vary, and differences in procedures for extraction, processing, and storage may also affect purity of the product and inconsistency in the package product.

Polyphenols are divided into different groups depending on the number of phenol rings and the chemical groups attached to the rings. Flavonoids make up the largest and the most important single group of polyphenols and can be divided into subgroups such as flavanols (catechin, epicatechin), flavonols (quercetin, myricetin, kaempferol), flavanons (hesperetin, naringenin), flavons (apigenin, luteolin), isoflavonoids (genistein, daidzein) and anthocyanins (cyaniding, malvidin). The capacity of flavonoids to act as an antioxidant is dependent upon their molecular structure, the position of hydroxyl groups and other substitutions in the chemical structure of these polyphenols. A number of excellent reviews dealing with their structure, absorption, metabolism, and pharmacokinetics have been published (Bravo 1998, Ross & Kasum 2002, Manach & Donovan 2004). Besides scavenging free radicals, many phenolics also exhibit multiple biological properties, e.g. anti-inflammatory, anticancer, antiviral, antimicrobial, vasorelaxant, and anticlotting activities (Rahman *et al.* 2007). In general, these phenolic compounds are rapidly converted to their glucuronide derivatives upon ingestion and are transported to the circulatory system and different body organs including the brain. In recent years, a number of reviews have reported on neuroprotective effects of polyphenols in cell and animal models,(Wang *et al.* 2001, Dajas *et al.* 2003, Mandel & Youdim 2004, Simonyi et al. 2005). This review is limited to neuroprotective effects of resveratrol from grape and wine, curcumin from turmeric, apocynin from *Picrorhiza kurroa*, and epigallocatechin-3-gallate from green tea (Fig 1).

There is evidence that some phenolic compounds exert their mode of action and target different intracellular pathways on a concentration-dependent manner. For example, low dose of red wine polyphenols was shown to promote angiogenesis via activation of the Akt/PI3K/eNOS, p38MAPK pathway but not the NF-κB pathway. However, at high dose, they can be anti-angiogenic through inhibition of the Akt/PI3K/eNOS pathway and enhancing the NF-κB pathway (Baron-Menguy *et al.* 2007). Another example is epicatechin, which not only exerts antioxidant activity but also can modulate protein kinase signaling pathways, depending on the concentration of the compound administered. In the study by Schroeter et al. (Schroeter *et al.* 2007), epicatechin stimulated ERK- and PI3K-dependent CREB phosphorylation at low 100 – 300 nmol/L but this effect was no longer apparent at the higher concentration of 30 mumol/L. These dose effects may be important to explain the anti- versus pro-oxidant actions of the phenolics and differences in experimental outcomes from different laboratories. It is also important to recognize that results from studies of phenolic compounds in cell culture system may not correspond to their action in vivo (Halliwell 2008).

4-a. Resveratrol

Epidemiological studies have reported that despite consuming a fatty diet, the population with moderate wine consumption has a lower incidence of cardiovascular diseases. A widely held theory for the cardioprotective effects of the “French paradox” is the anti-platelet aggregation properties of compounds in red wine in preventing the development of atherosclerotic plaques. In recent years, studies further indicated that red wine and grape polyphenols may also offer protective effects against neurodegenerative diseases (Esposito *et al.* 2002, Simonyi *et al.* 2002, Sun *et al.* 1999a, Sun *et al.* 1999b). Studies from our laboratory provided evidence that dietary supplement of polyphenols extracted from grape skin and seeds could ameliorate oxidative damage in synaptic membranes in the brain induced by chronic alcohol consumption

(Sun et al. 1999a, Sun et al. 1999b). Grape polyphenols also prevented chronic ethanol-induced increase in COX-2 mRNA expression in the rat brain (Simonyi et al. 2002).

Although grape also contains other types of polyphenols, trans-resveratrol (3,4′,5-trihydroxystilbene) is considered the most effective compound in producing beneficial health effects. In addition to grapes, resveratrol is found in a variety of plant species including peanuts and berries (Baur & Sinclair 2006). Resveratrol is also highly concentrated in some oriental herbal plants, such as kojo-kan, *polygonum caspidatum*, which is used to treat fevers, hyperlipidemia, atherosclerosis, and inflammation (Chung *et al.* 1992). In our studies with PC-12 cells, resveratrol was more effective in protecting against oxidative damage than vitamins E and C combined (Chanvitayapongs *et al.* 1997). A number of studies using cell models have provided information for the underlying mechanisms for neuroprotective effects of resveratrol (Gao *et al.* 2006a, Gao *et al.* 2006b, Lu *et al.* 2006, Raval *et al.* 2006, Cho *et al.* 2008, Tsai *et al.* 2007). Studies with cell culture models of Parkinson's disease also demonstrated neuroprotective effects of resveratrol in alleviating oxidative damage induced by neurotoxins (Gelinas & Martinoli 2002, Alvira *et al.* 2007).

Studies from our laboratory demonstrated the ability for resveratrol to protect against ischemia-induced DND in the gerbil global ischemia model (Wang et al. 2002) and neuronal excitotoxicity in rats induced by kainic acid (Wang *et al.* 2005c). The neuroprotective effects of resveratrol can be demonstrated by different mode of administration, e.g., by i.p. injection and by supplementing as grape powder formulation (Wang *et al.* 2005a).

Studies to examine bioavailability of resveratrol indicated that this compound is rapidly conjugated to its glucuronide derivative which is probably the vehicle for transportation to the circulatory system. Apparently, this form of resveratrol can readily cross the blood brain barrier albeit at lower levels when compared to that in the liver (Wang et al. 2002).

Besides excellent free radical scavenger properties, resveratrol can offer other effects to the cell, e.g., increasing the lifespan in yeast (Howitz *et al.* 2003). This effect is explained by its ability to activate sirtuins, which belong to a conserved family of NAD^+-dependent deacetylases (class III histone deacetylases) (Baur & Sinclair 2006). In the lower organisms including yeast, C elegans, and flies, increase in sirtuins is associated with extended lifespan. The multiple roles of resveratrol as an antioxidant and as a life-promoting agent make it an attractive candidate for treatment of neurodegenerative diseases (Anekonda 2006, Mancuso et al. 2007, Baur & Sinclair 2006).

Several studies demonstrated the ability for resveratrol to protect neurons against Abeta-induced toxicity in vitro (Chen *et al.* 2005, Han *et al.* 2004, Jang & Surh 2003). In fact, resveratrol combined with other polyphenolic compounds, such as catechin from green tea, can produce synergism in the protective effects (Conte *et al.* 2003a, Conte *et al.* 2003b). In a rat model of sporadic AD, chronic administration of resveratrol ameliorated the cognitive impairment and oxidative damage induced by intracerebroventricular injection of streptozotocin (Sharma & Gupta 2002). Red wine consumption also significantly attenuated AD-type deterioration of spatial memory function and Abeta neuropathology in Tg2576 mice (Wang *et al.* 2006a). There is evidence that resveratrol can inhibit formation and extension of Abeta fibrils and destabilize the fibrilized Abeta (Ono *et al.* 2006, Ono & Yamada 2006). Another study demonstrated its ability to reduce Abeta secretion in several cell lines via a mechanism that involves the proteasome (Marambaud *et al.* 2005).

A number of studies have demonstrated the ability of resveratrol to suppress neuroinflammatory responses, e.g., attenuating iNOS and COX-2 expression (Bi *et al.* 2005, Kim *et al.* 2007, Kim *et al.* 2006). However, it is not clear whether this action is related to the ability of resveratrol to minimize ROS production from NADPH oxidase. Consequently,

despite strong evidence for therapeutic potential of resveratrol for treatment of cancer, angiogenesis, myocardial infarction as well as different neurodegenerative diseases (Baur & Sinclair 2006), more investigations are needed to understand proper usage of this polyphenol and its mechanism of action on different cell types.

4-b. Curcumin

Curcumin (diferuloylmethane) is derived from turmeric, the powdered rhizome of the medicinal plant *Curcuma longa Linn*. It has been used for centuries throughout Asia as a food additive and a traditional herbal medicine. Recent studies demonstrated that besides potent antioxidative and anti-inflammatory properties of curcumin, it also exhibits anti-amyloidogenic effects (Ono *et al.* 2004). Curcumin can bind amyloid directly and inhibit Abeta aggregation as well as prevent fibril and oligomer formation (Yang *et al.* 2005). These anti-fibril effects of curcumin were also evidenced in studies with alpha synuclein, the protein involved in PD (Ono & Yamada 2006).

Curcumin supplementation has been recently considered as an alternative, nutritional approach to reduce oxidative, inflammatory damage and amyloid pathology associated with AD (Wu *et al.* 2006). However, because curcumin is common in many curry spices and is widely consumed by different populations, it is difficult for well designed studies to evaluate health effects of this polyphenol. When conventional NSAID, ibuprofen, and curcumin were compared for their ability to protect against Abeta-induced damage, dietary curcumin, not ibuprofen, was shown to suppress oxidative damage and reduced synaptophysin loss (Frautschy *et al.* 2001). Dietary curcumin also prevented Abeta-induced spatial memory deficits in the Morris water maze and post-synaptic density loss and reduced Abeta deposits (Frautschy et al. 2001). To evaluate whether curcumin could affect Alzheimer-like pathology in Tg2576 mice, both low and high doses of curcumin significantly lowered oxidized proteins and interleukin-1β, a proinflammatory cytokine elevated in the brains of these mice (Lim *et al.* 2001). Beside its anti-amyloid properties, curcumin can also offer antioxidant, anti-inflammatory and cholesterol lowering properties, all are important on ameliorating the deleterious consequences of AD (Ringman et al. 2005). Several clinical trials are in progress to address safety, tolerability, and bioavailability of this compound (Ringman et al. 2005, Fiala *et al.* 2007).

Besides AD, there is *in vitro* and *in vivo* data suggesting that curcumin exerts a protective effect against neurodegeneration in cerebral ischemia and Parkinson's disease. In a study in which curcumin was administered through i.v. injection (1 and 2 mg/kg) after focal ischemia, the neuroprotective effects were attributed to a protection of blood-brain barrier integrity (Jiang *et al.* 2007). In our laboratory, curcumin administered either through i.p. injection (30 mg/kg) or through a dietary supplementation (2.0 g/kg diet) for 2 months indicated significantly attenuated ischemia-induced DND as well as glial cell activation in the gerbil model (Wang et al. 2005b). Most interestingly, curcumin administration not only reduced ischemia-induced lipid peroxidation and mitochondrial dysfunction, it also ameliorated the increase in locomotor activity observed at 24 hour after ischemic insult, thus correlating behavioral deficits with the extent of neuronal damage (Wang et al. 2005b). Consistent with other studies, bioavailability study indicated a rapid increase in curcumin in plasma and other body organs including the brain within 1 hour after i.p. injection (Ringman et al. 2005, Goel *et al.* 2008).

The neuroprotective effects of curcumin relavant to PD are likely to be associated with its antioxidant and anti-inflammatory properties (Chen & Le 2006, Jagatha *et al.* 2008, Zbarsky *et al.* 2005). As found for Abeta, curcumin also can inhibit aggregation of alpha-synuclein (Pandey *et al.* 2008). Recent studies have identified other molecular targets of curcumin, including its action on transcription factors, growth factors, antioxidant enzymes, cell-survival kinases and signaling molecules (Ramassamy 2006, Salvioli *et al.* 2007, Goel *et al.* 2008). On the other hand, it is worth noting that excessive application of curcumin may produce pro-

oxidative effects (Ahsan *et al.* 1999). Therefore, more studies are needed to understand the different modes of action of curcumin on specific enzymes and pathways prior to recommendation for its use as a therapeutic agent.

4-c. Apocynin

Apocynin (4-hydroxy-3-methoxy-acetophenone) was discovered during activity-guided isolation of immunomodulatory constituents from *Picrorhiza kurroa*, a creeping plant native to the mountains of India, Nepal, Tibet and Pakistan (*Picrorhiza kurroa*, Monograph, 2001). *Picrorhiza kurroa* has been used as an herbal medicine for centuries for treatment of a number of inflammatory diseases. Apocynin may also be obtained from other sources, e.g. from the rhizome of Canadian hemp (*Apocymum cannabinum*), other Apocynum species (e.g. *A. androsaemifolium*) or from the rhizomes of *Iris* species. This compound has been regarded as a powerful anti-oxidant and anti-inflammatory agent, specifically, for blocking the activity of NADPH oxidase through interfering with the assembly of the cytosolic NADPH oxidase components with its membrane components (Stolk *et al.* 1994).

NADPH oxidase is increasingly recognized for its dual-edge roles in health and disease and has been implicated in the pathogenesis of many diseases, including cardiovascular and neurodegenerative diseases (Bedard & Krause 2007). In recent years, it has become apparent that brain cells constitutively express a superoxide-generating enzyme analogous to the NADPH oxidase in phagocytes (Infanger *et al.* 2006). The prototypic NADPH oxidase comprises a membrane-associated cytochrome b558 with one p22 phox and one gp91 phox subunit and several regulatory cytosolic subunits (p47 phox, p40 phox, p67 phox and the small G protein Rac1 or Rac2). Upon phosphorylation, the cytosolic subunits are translocated to bind with the membrane subunits. Consequently, a number of receptor-signaling pathways are linked to activation of NADPH oxidase leading to rapid production of superoxide anions (Bedard & Krause 2007).

Altered NADPH oxidase function has been linked to neurological disorders such as stroke, Alzheimer's and Parkinson's diseases (Lambeth 2007). Several reports of human studies (on AD, PD and stroke) demonstrated upregulation of different subunits expression in microglial cells (Wu et al. 2003). Genetic deletion of gp91phox mitigates neuronal loss in a variety of animal models of neurodegeneration, including the MPTP model of PD and cerebral ischemia (Zhang *et al.* 2004). Apocynin has been effective in ameliorating neuropathological damages in both *in vivo* and *in vitro* models of PD (Anantharam *et al.* 2007, Gao *et al.* 2003a, Gao *et al.* 2003c, Gao et al. 2003b). Apocynin also retarded disease progression and extended survival in a mouse ALS model (Boillee & Cleveland 2008). Immunohistochemical studies demonstrated that the increase in NADPH oxidase subunits expression after transient focal cerebral ischemia is mainly derived from activated microglial cells. Apocynin was effective in preventing ischemic damage and blood-brain barrier disruption in different animal models of experimental stroke (Wang *et al.* 2006b, Tang *et al.* 2007, Kahles *et al.* 2007). In our study using the gerbil global cerebral ischemia model, apocynin inhibited ischemia/reperfusion-induced increase in lipid peroxidation, oxidative DNA damage, and glial cell activation in the hippocampus (Wang et al. 2006b).

NADPH oxidase-dependent production of superoxide radicals has been identified as a major contributor to oxidative and inflammatory responses in the brain under different injury conditions. Activation of NADPH oxidase in glial cells is linked to increased secretion of cytokines and other inflammatory factors (Dringen 2005). Superoxide produced from NADPH oxidase may interact with nitric oxide from iNOS to form the toxic peroxynitrite, which is considered an important factor associated with neuronal death (Brown 2007). Aside from suppressing NF-κB pathway and preventing COX-2 expression in activated monocytes (Barbieri *et al.* 2004), apocynin is also effective against Abeta-induced microglial proliferation

and lipopolysaccharide (LPS) and interferon γ-induced neuronal death (Li *et al.* 2004, Jekabsone *et al.* 2006, Shibata *et al.* 2006).

An apparent limitation for therapeutic use of apocynin is the high concentrations needed for exerting beneficial effects. Furthermore, most studies have used acute treatment and few studies employed a preventative, dietary approach. In vitro studies suggest that apocynin may be converted to diapocynin through chemical catalysis using ferrous sulfate and sodium persulfate or through peroxidases such as myeloperoxidase. However, our recent study failed to detect diapocynin in rat plasma and tissues after systemic injection of apocynin (Wang *et al.* 2007a). However, our study on bioavailability showed that similar to other polyphenols, apocynin is rapidly converted to its glucuronide derivative and transported to the circulation system and other body organs, including the brain. More studies are necessary for considering the potential therapeutic use of apocynin for treatment of neurodegenerative disorders.

4-d. Other natural phenolics

Many other phenolic compounds in fruits and vegetables are good candidates for consideration as therapeutics in combating aging and neurodegenerative diseases (Vauzour *et al.* 2007). Among these, there is special interest regarding the neuroprotective actions of (−)-epigallocatechin-3- gallate (EGCG) from green tea (Sutherland *et al.* 2006). Besides its free radical scavenging, iron chelating, and anti-inflammatory properties, EGCG can exert its action on different sites of the apoptotic pathways, including altering the expression of anti- and pro-apoptotic genes. These studies further implicate that green tea extract may also exert protection through controlling calcium homeostasis, activation of MAPK, PKC, antioxidant enzymes, survival genes and modulating enzymes for processing of the amyloid precursor protein (Mandel *et al.* 2004, Mandel & Youdim 2004, Weinreb *et al.* 2008). EGCG was shown to inhibit 6-OHDA-induced NF-kB-mediated expression of cell death and cell cycle genes (Levites *et al.* 2002a, Levites *et al.* 2002b).

In light of the neuroprotective effects from different polyphenols and plant extracts, a summary of recent studies describing neuroprotective effects of different botanical compounds in different animal models for AD, PD, and stroke is provided in Table 1. Amentoflavonoid, a naturally occurring bioflavonoid, was able to rescue neurons from hypoxic-ischemic injury (Shin *et al.* 2006,Yi *et al.* 2006). This compound seems to implement multiple mechanisms including direct blockade of cell death cascades and anti-inflammatory inhibition of microglial. Coenzyme Q (CoQ) is enriched in a number of diets and is a potent antioxidant. This redox active compound has been implicated to play an important role in improving mitochondrial function. However, whether CoQ(10) can be used as a therapeutic agent for treatment of PD remains to be investigated (Storch *et al.* 2007).

5. Botanical phenolics on intracellular signaling pathways

It is becoming recognized that besides their anti-oxidative and anti-inflammatory properties, many phenolics may also have specific action on intracellular signaling pathways (Fig 2). These signaling pathways are interrelated and are evolved form ROS from NADPH oxidase and mitochondria. In particular, these signaling pathways are downstream of ROS produced from NADPH oxidase upon injury due to cerebral ischemia, Abeta and excitotoxicity. In our studies, we further link these kinases to activation of $cPLA_2$ and release of arachidonic acid. There is also evidence that ROS produced from NADPH oxidase is linked to transcriptional pathways, such as the NF-κB pathway and the Nrf/ARE pathway for induction of antioxidant and inflammatory genes (Santangelo *et al.* 2007) and subsequently, triggering the apoptotic pathway (Zhu et al. 2006). Successful identification of these compounds and their action on intracellular signaling pathways will be important for effective use to combat neurodegenerative diseases.

6. Concluding Remarks

Despite complex and diverse genetic and epi-genetic factors underlying manifestations of different neurodegenerative diseases, there are strong reasons to believe that oxidative stress is a common factor playing a central role in the pathogenesis of these diseases. While many pathological conditions are associated to ROS production from mitochondria, more recent studies have unveiled an important role of ROS from NADPH oxidase. Studies here indicate that phenolic compounds such as resveratrol from grape and wine, curcumin from turmeric, epigallocatechin from green tea, and apocynin from *Picrorhiza kurroa*, not only exhibit potent antioxidative properties for scavenging free radicals, but may also act on specific signaling pathways for regulating inflammatory responses. These studies support the use of plant-derived phenolic supplements in promoting general health and prevent against age-related diseases in humans.

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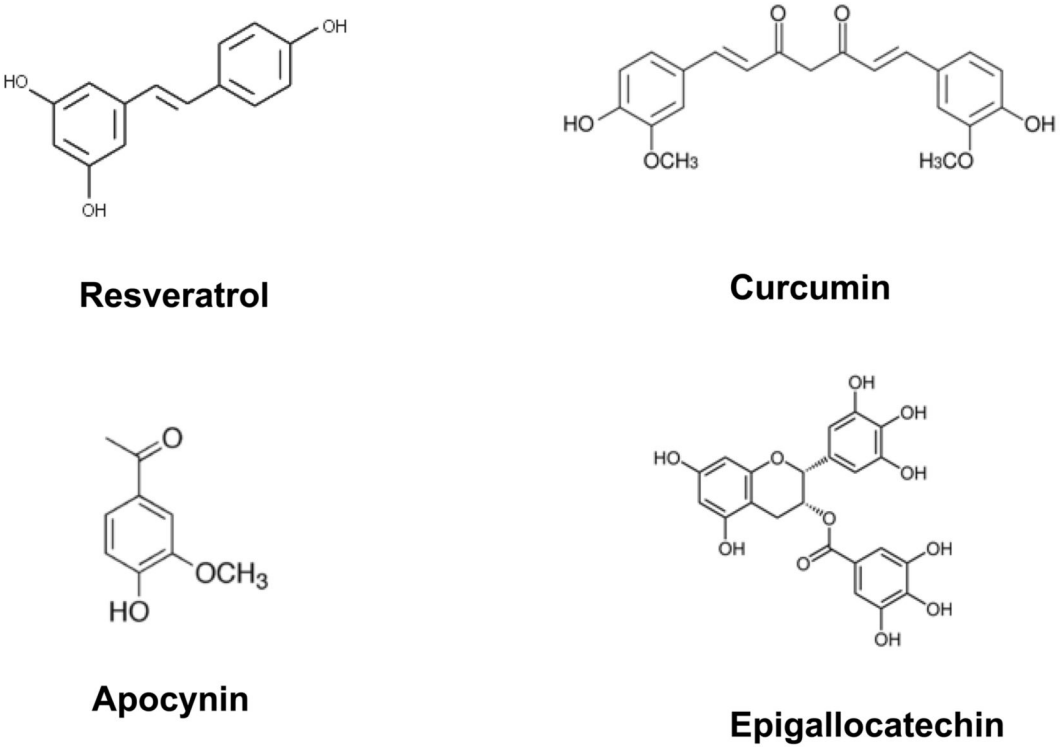

Fig 1.
Structure of resveratrol, curcumin, apocynin and epigallocatechin-gallate

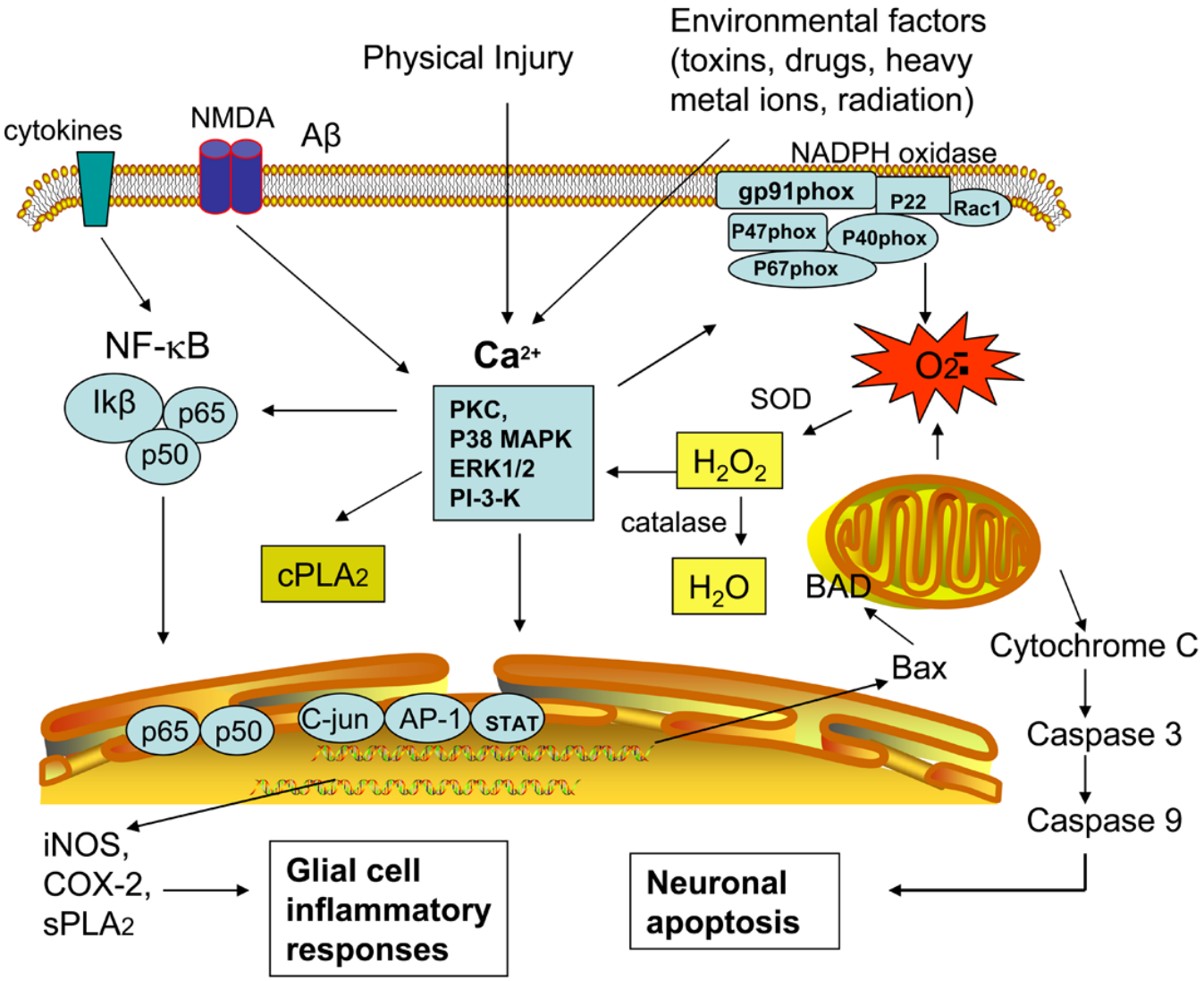

Fig 2.
Signaling pathways associated with oxidative stress

Table 1

Effects of common botanicals on AD, PD and stroke

Polyphenol/plant name	Model	Effects	References
AD models			
Blueberry	Tg2576 mice	+	(Joseph et al. 2003)
EGCG	Tg2576 mice	+	(Rezai-Zadeh et al. 2005)
Garlic	Tg2576 mice	+	(Chauhan 2003) (Chauhan 2006)
	TgCRND8 mice	+	(Chauhan & Sandoval 2007)
Ginkgo biloba	Tg2576 mice	+	(Stackman et al. 2003)
	TgAPP/PS1 mice	+	(Garcia-Alloza et al. 2006) (Tchantchou et al. 2007)
Ginseng	Tg2576 mice	+	(Chen et al. 2006)
Ginsenoside Rb1 or M1	Aβ infusion (i.c.v.) mice	+	(Tohda et al. 2004)
Pomegranate	Tg2576 mice	+	(Hartman et al. 2006)
PD models			
Black tea	6-OHDA rat	+	(Chaturvedi et al. 2006)
Cocoa	6-OHDA rat	−/+	(Datla et al. 2007)
EGCG	MPTP mice	+	(Choi *et al.* 2002) (Mandel & Youdim 2004)
Ginkgo biloba	6-OHDA rat	+	(Kim *et al.* 2004)
Grape seed	6-OHDA rat	−	(Datla et al. 2007)
Green tea	MPTP mice	+	(Choi et al. 2002)
	6-OHDA rat	+	(Guo et al. 2007)
Quercetin	6-OHDA rat	−	(Zbarsky et al. 2005)
Red clover	6-OHDA rat	+	(Datla et al. 2007)
Tangerine peel extract	6-OHDA rat	+	(Datla et al. 2007)
Stroke models			
Bluberries	rat permanent left CCAO+H	+	(Sweeney *et al.* 2002)
	rat transient MCAO	+	(Wang *et al.* 2005d)
Buckwheat polyphenols	rat repeated ischemia	+	(Pu et al. 2004)
Curcuma oil	rat transient MCAO	+	(Rathore et al. 2007)
Garlic	rat transient MCAO	+	(Saleem *et al.* 2006)
Ginseng	gerbil transient CCAO	+	(Shen & Zhang 2003)
Grape seed extract	neonatal rat H-I	+	(Feng *et al.* 2005, 2007)
Green tea extract	rat transient MCAO	+	(Hong et al. 2000)
	gerbil transient CCAO	+	(Hong et al. 2001)
Mulberry extract	mouse transient MCAO	+	(Kang et al. 2006)
Pomegranate	neonatal mouse H-I	+	(West et al. 2007)
Red wine polyphenols	rat transient MCAO	+	(Ritz et al. 2008)
Sesame oil	rat transient MCAO	+	(Ahmad et al. 2006)
Spinach	rat transient MCAO	+	(Wang et al. 2005d)