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Adaptive Cellular Stress Pathways as Therapeutic Targets of Dietary Phytochemicals: Focus on the Nervous System

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Abstract——**During the past 5 decades, it has been widely promulgated that the chemicals in plants that are good for health act as direct scavengers of free radicals. Here we review evidence that favors a different hypothesis for the health benefits of plant consumption, namely, that some phytochemicals exert disease-preventive and therapeutic actions by engaging one or more adaptive cellular response pathways in cells. The evolutionary basis for the latter mechanism is grounded in the fact that plants produce natural antifeedant/noxious chemicals that discourage insects and other organisms from eating them. However, in the amounts typically consumed by humans, the phytochemicals activate one or more conserved adaptive cellular stress response pathways and thereby enhance the ability of cells to resist injury and disease. Examples of such pathways include those involving the transcription factors nuclear factor erythroid 2-related factor 2, nuclear factor-κB, hypoxia-inducible factor 1α, peroxisome proliferator-activated receptor γ, and forkhead box subgroup O, as well as the production and action of trophic factors and hormones. Translational research to develop interventions that target these pathways may lead to new classes of therapeutic agents that act by stimulating adaptive stress response pathways to bolster endogenous defenses against tissue injury and disease. Because neurons are particularly sensitive to potentially noxious phytochemicals, we focus on the nervous system but also include findings from other cell types in which actions of phytochemicals on specific signal transduction pathways have been more thoroughly studied.**

I. Introduction

Epidemiologic studies have demonstrated significant associations of regular consumption of vegetables, fruits, tea leaves, and coffee with improved health outcomes, including reduced risk for cardiovascular disease, stroke, diabetes, some cancers, asthma, rheumatoid arthritis, and neurodegenerative disorders. The literature in this area is extensive and was recently reviewed (Schneider and Segre, 2009; Butt and Sultan, 2011; Boeing et al., 2012; Wedick et al., 2012; Martin et al., 2013). Thousands of studies have reported beneficial effects of administration of specific fruits and vegetables, their extracts, or chemicals isolated from the plants, in animal models of these and other diseases (Wang et al., 2005b; González-Gallego et al., 2010; Graf et al., 2010; Wahle et al., 2010; Yang et al., 2011a; Williams and Spencer, 2012). However, as is usually the case, the translation of the epidemiologic and preclinical data into clear results in clinical trials has been mostly unremarkable. Reasons for no or modest effects of such interventions in subjects who already have a disease are not established, but likely explanations include the following: 1) once the disease is fully manifest, the relatively modest hormetic actions of phytochemicals may not be capable of reversing the disease process; 2) the dosing approach for clinical trials typically involves sustained high-dose treatment, whereas experimental data suggest that intermittent lower doses may be more effective; 3) the duration of the human studies are typically very short (6–12 months) compared with the course of the development and progression of the disease; and 4) the magnitude of the disease-modifying actions of phytochemicals are often not dramatic, even in tightly controlled studies of isogenic strains of rodents. Therefore, small beneficial effects may not be evident in short-term studies and/or may be masked by the high interindividual variability among human subjects.

Because fruits and vegetables do contain antioxidant chemicals with free radical–scavenging activities, most of the research on phytochemicals and health during the past 50 years has focused on the idea that it is these "dietary antioxidants" that directly neutralize free radicals in cells throughout our body, thereby protecting against diseases. Indeed, the notion that phytochemicals can protect against disease by directly squelching oxygen free radicals remains a prominent theory in the fields of nutrition and chronic diseases (Seifried et al., 2007; Balsano and Alisi, 2009; Slavin and Lloyd, 2012). It is certainly the case that some phytochemicals, particularly phenolic compounds, can directly scavenge oxygen free radicals. However, micromolar concentrations of these phytochemicals are required to effectively scavenge free radicals, and such high concentrations have not been shown to be achieved by the consumption of fruits, vegetables, teas, or other dietary plants. Therefore, there is a clear problem with the antioxidant hypothesis for the health benefits of

ABBREVIATIONS: 3NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; Aβ, amyloid β-peptide; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; APP, β-amyloid precursor protein; BDNF, brain-derived neurotrophic factor; BPA, bisphenol A; CBP, CREB-binding protein; COX-2, cyclooxygenase-2; CREB, cAMP response element-binding protein; Cul, Cullin; EDC, endocrine-disrupting chemical; EGCG, epigallocatechin gallate; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; FOXO, forkhead box subgroup O; GDNF, glial cell line–derived neurotrophic factor; GSK, glycogen synthase kinase; HD, Huntington disease; HIF, hypoxia-inducible factor; HO, heme oxygenase; HPA, hypothalamic-pituitary-adrenal; Hsp, heat shock protein; IGF, insulin-like growth factor; IPC, ischemic preconditioning; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MHY 966, 2-bromo-4-(5-chloro-benzo[*d*]thiazol-2-yl) phenol; MMP, matrix metalloproteinase; MPP, 1-methyl-4-phenylpyridine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; NGF, nerve growth factor; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; P450, cytochrome P450; PD, Parkinson disease; PHD, prolyl hydroxylase; PI3K, phosphoinositol 3 kinase; PPAR, peroxisome proliferator–activated receptor; PPRE, peroxisome proliferator response element; pVHL, von Hippel-Lindau tumor suppressor protein; NQO1, NAD(P)H quinone oxidoreductase 1; ROS, reactive oxygen species; SH, sulfhydryl; SIRT, sirtuin; SOD, superoxide dismutase.

phytochemicals. Moreover, the emerging evidence suggests that very high doses of antioxidant vitamins may not be beneficial for health and might even be harmful. Indeed, clinical trials of vitamins E, C, and A have failed in patients with a range of disorders (Hasnain and Mooradian, 2004; Block et al., 2007; Canter et al., 2007; Maserejian et al., 2007; Galasko et al., 2012).

Reports recently began appearing in the literature suggesting that at least some of the chemicals in fruits, vegetables, and other plants may prevent or mitigate various chronic diseases by activating adaptive stress response signaling pathways in cells (Trewavas and Stewart, 2003; Mattson and Cheng, 2006). This "hormesis hypothesis" posits that cells throughout the body and brain recognize some phytochemicals as potentially dangerous, and thus respond adaptively by engaging one or more stress signaling pathways that enhance the resistance of cells, organs, and the organism to a range of stressors that can cause or promulgate disease(s). A working definition of hormesis is "a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces an adaptive beneficial effect on the cell or organism" (p. 1; Mattson, 2008). When plotted on a graph, hormesis manifests as a biphasic dose-response curve, with low doses exerting a stimulatory or beneficial effect and progressively higher doses resulting in toxicity and even death.

Throughout this review, we use the term *phytochemical* to refer to any chemical isolated from a plant. Many of the most effective and widely used drugs are either naturally occurring phytochemicals or analogs thereof (Newman and Cragg, 2009, 2012). Prominent examples include antibiotics based on penicillin and tetracycline, statins based on 7-methyl monacolin A from *Monascus ruber*, antitumor drugs based on paclitaxel from *Taxus brevifolia* or rapamycin from *Streptomyces hydroscopicus*, and pain medications based on morphine from *Papaver somniferum*. Some of these major drugs act to induce stress in target cells at a level that preferentially kills unwanted cells (e.g., bacteria in infections and tumor cells in cancers). Other widely used phytochemical-based drugs and dietary supplements may act by stimulating adaptive stress responses in somatic cells affected by disease. Indeed, emerging evidence suggests that this may be true for drugs previously thought to act by a more specific mechanism. For example, statins reduce cholesterol production but also enhance nitric oxide (NO) signaling, antioxidant defenses, and anti-inflammatory pathways, which may contribute to suppression of atherosclerotic plaque formation (Davignon, 2004). Another example is caffeine, which is perhaps the most widely ingested neuroactive phytochemical and clearly induces adaptive stress responses in neurons and other cells; this may be a general mechanism to explain the increasingly recognized health benefits of consumption of moderate amounts of caffeine (Heckman et al., 2010). This article reviews our current understanding of phytochemicals that induce adaptive cellular stress responses, as well as the signaling pathways and effector molecules they regulate.

II. Evolutionary Considerations

To fully appreciate the responses of animal cells to phytochemicals, it is valuable to understand the reasons those phytochemicals are present in plants. Plants are a major food source for a wide range of species of insects, birds, and mammals. During the course of evolution, complex relationships developed between plants and animals. In some cases, plants benefit from animals. For example, birds and mammals can facilitate seed dispersion and thereby expand the range of a plant. On the other hand, plants have evolved a range of structural and chemical defenses to protect themselves from destruction by animals. In this section, we describe the evolution of noxious phytochemicals, as well as the counterevolution in animals of pathways for the metabolism and adaptive cellular responses to phytochemicals.

Plants deploy several evolutionarily conserved mechanisms to protect themselves from being ravaged by organisms ranging from insects to mammals. One strategy is the development of structural barriers such as bark and thorns. A second strategy is the production of chemicals that are noxious to organisms in one or more ways. These phytochemicals are variously termed *natural pesticides*, *biopesticides*, or *insect antifeedants* (Koul, 2005). In most cases, the noxious phytochemicals are sensed by the nervous system of the organism via taste, olfactory, or pain receptors, and the organism responds by refraining from eating that part of the plant. The noxious phytochemicals are often concentrated in certain cell types and structures of the plants that are most exposed to the environment and/or are critical for reproduction, including buds, seeds, and the skin of fruits. Such phytochemicals typically activate taste receptors for bitter chemicals and are the reason humans usually do not eat the "peels" of citrus fruits and bananas. These natural pesticides are produced as secondary metabolites within the plant cells or, in some cases, by endophytic bacteria or fungi (Bascom-Slack et al., 2012). Thousands of natural pesticides have been isolated from plants, with most of them falling into a major structural category such as alkaloids, terpenoids, flavonoids, and isothiocyanates (Schmutterer, 1990; Klein Gebbinck et al., 2002).

It is important to recognize that from an evolutionary perspective, it is likely that many phytochemicals that elicit neurobiological responses in animals and humans evolved as feeding deterrents. These include psychoactive phytochemicals (Fig. 1) such as cannabinoids, mescaline, psilocybin, and salvinorin A (Brawley and Duffield, 1972); spices such as curcumin and capsaicin

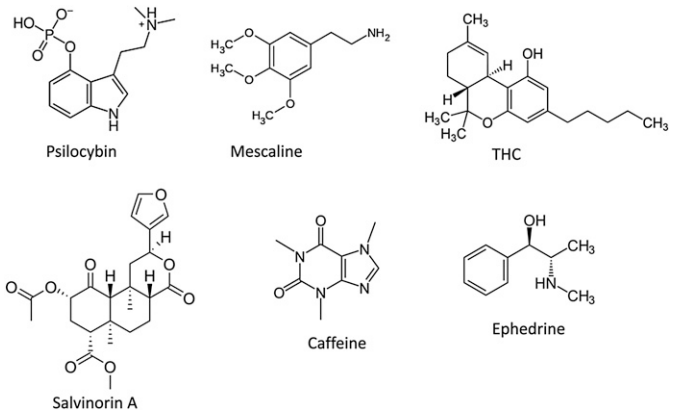

Fig. 1. Structures of representative psychoactive phytochemicals. THC, tetrahydrocannabinol.

(Aggarwal et al., 2008); and stimulants such as caffeine and ephedrine (Magkos and Kavouras, 2004). Although the rapid and overt responses upon ingestion or inhalation of these chemicals are manifest in neurons of the peripheral and/or central nervous systems, cells in other organs also respond in many cases. For example, cannabinoids can act directly on pancreatic β cells to alter their proliferation (Kim et al., 2011b) and curcumin acts on lymphocytes to modulate inflammation (Gautam et al., 2007).

Organisms that consume plants have evolved numerous enzymes to degrade potentially toxic phytochemicals, a process that typically involves three phases: 1) phase I enzymes add reactive and polar groups to the phytochemical, with hydroxylation by cytochrome P450 (P450)–dependent oxidases being the most prevalent; 2) phase II enzymes catalyze the conjugation of a carboxyl, hydroxyl, amino, or sulfhydryl (SH) group on the phytochemical with a charged molecule such as glucuronic acid or glutathione; and 3) phase III enzymes catalyze the ATP-dependent transport of the conjugated phytochemical outside of the cell, where it is then further metabolized or excreted (Iyanagi, 2007). Phase I and II enzymes are present in high amounts in hepatocytes that process circulating phytochemicals and drugs, but are also expressed in cells of organ systems that are more directly exposed to the chemicals including the gut, lungs, and skin (Zhang et al., 2006; Baron et al., 2008; Thelen and Dressman, 2009). Because of the existence of these efficient mechanisms for detoxifying and eliminating potentially harmful phytochemicals, cells are exposed only transiently to the phytochemicals. This contrasts with some human-made pesticides such as dichlorodiphenyltrichloroethane, for which metabolizing enzymes have not evolved and thus the chemical accumulates in toxic amounts. Nevertheless, the concentration of a particular noxious phytochemical in a plant can limit the amount that plant consumed in a given time period. Indeed, the diets of vertebrate herbivores are restricted by mechanisms that regulate the intake, absorption, and detoxification of chemicals in the plants they consume (Lappin, 2002; Foley and Moore, 2005).

Much as we live with commensal microorganisms (bacteria and fungi) on our skin and in our gut (Kamada et al., 2013; Schommer and Gallo, 2013), higher plants coexist with fungi and bacteria that live among their cells (Reinhold-Hurek and Hurek, 2011; Mousa and Raizada, 2013). Although many phytochemicals are produced by plant cells, others are produced by the fungi or bacteria that live within the plant (Bascom-Slack et al., 2012). As with the mammalian "microbiome," the plant microbiome plays critical roles in maintaining the health of the organism. Importantly, the microorganisms living within a plant (endophytes) produce chemicals that help protect that plant against pathogenic microorganisms, insects, and other organisms that would otherwise eat/destroy the plant (Verma et al., 2009; Reinhold-Hurek and Hurek, 2011; Mousa and Raizada, 2013). In many instances, fungi and bacteria living within a plant have evolved to produce chemicals that increase the resistance of that plant to a broad range of stressors, thereby enhancing the fitness and survival of the plant (Fig. 2). These phytoprotective chemicals include a range of structures with prominent categories, including alkaloids, terpenoids, flavonoids, phenolic compounds, polyketides, and phenylpropanoids (Strobel et al., 2004; Qin et al., 2011; Gutierrez et al., 2012; Aly et al., 2013; Mousa and Raizada, 2013).

There are prominent examples of therapeutically effective phytochemicals that are shown to be produced by endophytes and not the cells of the plant they

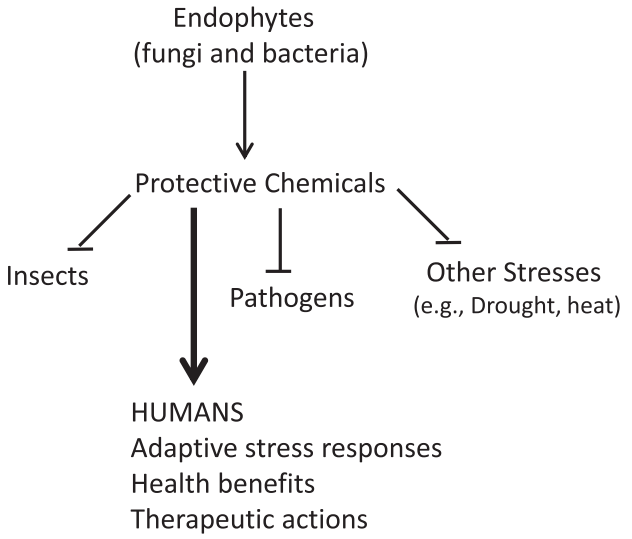

Fig. 2. Endophyte-derived chemicals enhance stress resistance of plants. Bacteria and fungi that live within plants in a symbiotic or commensal relationship (endophytes) produce chemicals that protect the plants from infectious agents, pests, and physical stressors such as drought and extreme temperatures. By stimulating adaptive stress response signaling pathways in cells, some of these endophyte-derived phytochemicals may have beneficial effects on human health.

inhabit. Paclitaxel (Taxol) was originally isolated from the Pacific yew, and has since shown to be produced by endophytic fungi (*Taxomyces andreanae*) that colonize the yew (Stierle et al., 1993). Paclitaxel has proven to be an effective drug in the armamentarium of chemotherapeutic agents for cancer patients. Mevinolin (Lovastatin) is a fungal metabolite isolated from *Aspergillus terreus* that is a naturally occurring inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase, a key enzyme in cholesterol biosynthesis (Alberts et al., 1980). This endophytic phytochemical is now among the most widely prescribed class of drugs (statins) for reducing the risk for cardiovascular disease in hypercholesterolemic patients. Endophytic bacteria and fungi typically produce chemicals that have antimicrobial activity, which is a mechanism for preventing pathogenic bacteria and fungi from destroying their host plant. Most of the commonly used antibiotics are produced by bacteria or fungi that are either endophytes or saprophytes; these include erythromycin (from the bacteria *Saccharopolyspora erythraea*), penicillin (from the *Penicillium* genus of ascoycetous fungi), and tetracycline (from the *Streptomyces* genus of actinobacteria).

III. Hormesis and the Biphasic Dose Response to Phytochemicals

A highly conserved feature of the responses of cells and organisms to phytochemicals is that they are biphasic (Fig. 3). Most commonly, exposure to low doses results in stimulatory/beneficial effects, whereas exposure to high doses has inhibitory/detrimental effects. Exposure of cells and organisms to low doses of chemicals that are toxic at higher doses often triggers adaptive stress responses that can protect against higher doses of the same chemical and, importantly, a range of different stressors. This general biologic phenomenon, which is termed *hormesis*, is firmly engrained in the evolutionary history of all organisms (Calabrese et al., 2007; Mattson, 2008; Calabrese and Mattson, 2011). In some cases, organisms have even incorporated once-toxic environmental agents into their own macromolecules where they serve important functions. Prominent examples of how hormetic mechanisms have shaped evolution include the metals iron, copper, and selenium. In their free ionic forms, iron (Fe^{2+}) and copper (Cu^{+}) are toxic to cells because they catalyze the generation of the highly reactive hydroxyl free radical (Brewer, 2007). However, organisms have evolved numerous iron- and copper-binding proteins that sequester Fe^{2+} and Cu^{+} (Sargent et al., 2005; Rubino and Franz, 2012). Moreover, Fe and Cu play important roles in the function of some proteins, including hemoglobin, iron-sulfur cluster proteins, and antioxidant enzymes (Abreu and Cabelli, 2010; Kakar et al., 2010; Rouault, 2012). The history of selenium and health provides another excellent example of evolutionary hormesis. Selenium was originally found to be toxic to animals when ingested at moderately high concentrations (Frost and Lish, 1975). It was subsequently discovered that small amounts of selenium are required for optimal health and survival of many organisms, including humans (Rayman, 2012). Selenium is incorporated into several different proteins (selenoproteins) that serve antioxidant and other beneficial functions in cells, thereby protecting the cells and organisms against injury and disease (Fairweather-Tait et al., 2011).

Organisms have evolved numerous adaptive cellular stress response pathways that are engaged by environmental stressors ranging from heat and drought to food deprivation and many phytochemicals (as described below). Because of the criticality of obtaining energy and nutrients, organisms have developed the ability to consume plants that produce a myriad of natural biopesticides (Koul, 2005). One mechanism by which organisms manage such potentially toxic phytochemicals is to rapidly metabolize them and eliminate

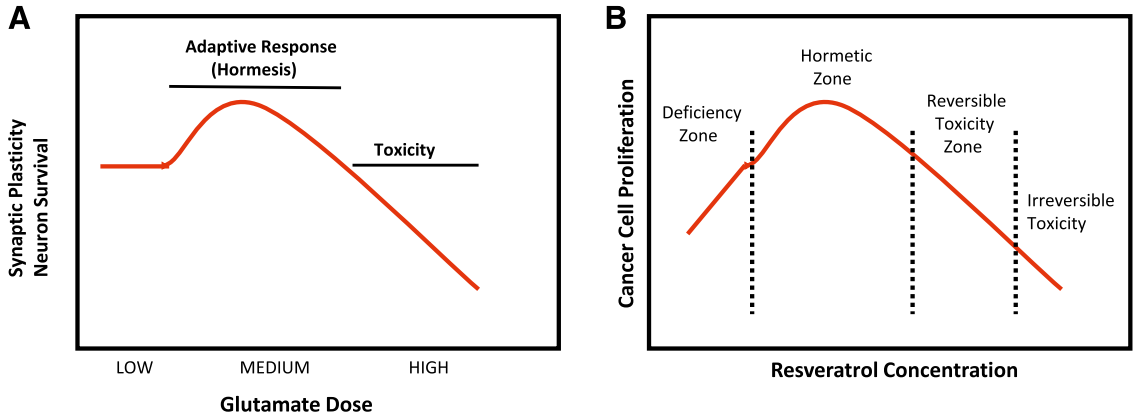

Fig. 3. Endogenous signaling molecules and phytochemicals often elicit biphasic dose responses on cells and organisms. (A) Glutamate is the major excitatory neurotransmitter in the brain of all mammals. Neurons respond to moderate levels of glutamate by enhancing the plasticity of synapses, a process that is critical for learning and memory. High levels of glutamate cause degeneration of synapses and the death of neurons. (B) Low levels of resveratrol can enhance cancer cell proliferation, whereas higher levels inhibit cell proliferation and may even trigger cell death. Adapted from Mattson and Calabrese (2010) and Calabrese et al. (2010).

them in the urine. "Detoxifying enzymes" called P450s in the liver and elsewhere are the major means of removing phytochemicals (Guengerich and Cheng, 2011). Another mechanism is the activation of one or more adaptive cellular stress response signaling pathways by the phytochemical, which is the topic of this review. For example, exposure of neurons to sulforaphane (present in high amounts in broccoli), curcumin (an Indian spice from the turmeric root), or allicin (from garlic) can protect the neurons against a range of metabolic, chemical, and oxidative insults (Bautista et al., 2005; Scapagnini et al., 2006; Han et al., 2007). However, high concentrations of all of the latter phytochemicals can damage and kill neurons, demonstrating a typical biphasic hormesis-based dose-response curve. Fortunately, phytochemicals that are safely consumed by animals, including humans, typically activate adaptive stress responses at low concentrations, exert noxious but nontoxic effects at somewhat higher concentrations, and are only toxic at very high concentrations. Thus, noxious effects (e.g., nausea) usually occur well before a toxic amount is consumed, thereby preventing an "overdose."

IV. Phytochemicals and Cellular Stress Resistance

Exposure of cells to low doses of phytochemicals can, in many cases, increase the resistance of the cells to a range of stressors. Four general types of cellular stress that are relevant to the pathogenesis of most major chronic diseases are as follows: 1) oxidative stress resulting from increased production or reduced removal/detoxification of oxygen free radicals (Yorek, 2003); 2) metabolic stress resulting from impaired cellular bioenergetics and mitochondrial function (Bratic and Trifunovic, 2010); 3) proteotoxic stress in which damaged and misfolded proteins aggregate and accumulate in cells, such as the proteins τ and α-synuclein that accumulate in neurons in Alzheimer disease (AD) and Parkinson disease (PD), respectively (Mattson, 2004; Kalia et al., 2013); and 4) inflammatory stress involving innate and humoral immune cells that produce damaging reactive oxygen species (ROS) and cytokines (Xu, 2013). This section reviews studies that have demonstrated cytoprotective effects of phytochemicals in experimental models involving the latter four types of stressors.

A. Oxidative Stress

ROS are continuously produced in all cells, with the major source being superoxide anion radicals generated by the mitochondrial electron transport chain (particularly complexes I and III) during oxidative phosphorylation. Superoxide is also generated by various oxidases, including xanthine oxidase and NAD(P)H oxidases (Sakellariou et al., 2014). Superoxide is converted to hydrogen peroxide by superoxide dismutases (SODs) located in the mitochondria (Mn-SOD/SOD2) and cytoplasm (Cu/Zn-SOD/SOD1). Hydrogen peroxide can be completely detoxified by catalase and glutathione peroxidases. However, in the presence of even very low amounts of Fe^{2+} or Cu^{+}, hydrogen peroxide is converted via the Fenton reaction to hydroxyl radicals that can attack double bonds in membrane lipids, resulting in an autocatalytic process called lipid peroxidation (Mattson, 2009). Another prominent ROS is NO, which is generated by NO synthase in response to an elevation of intracellular Ca^{2+} levels. NO can interact with superoxide to produce peroxynitrite that, similar to the hydroxyl radical, induces membrane lipid peroxidation. 4-Hydroxynonenal, an aldehyde liberated during lipid peroxidation, can impair cellular function and trigger apoptosis by covalently modifying various proteins (Mattson, 2009). Glutathione, a 3-amino acid peptide with a cysteine residue, is an important endogenous "detoxifier" of 4-hydroxynonenal (Balogh and Atkins, 2011).

Excessive accumulation of oxidatively damaged molecules is a common feature of the most prevalent and fatal diseases, including cardiovascular disease, diabetes, cancers, and neurodegenerative disorders (e.g., AD and PD). Aging is a major risk factor for each of these chronic diseases. Accordingly, the accumulation of oxidatively damaged proteins, nucleic acids, and membranes that occurs during normal aging is believed to be accelerated in these diseases. Genetic predispositions and environmental factors, particularly diet and lifestyle, determine whether any particular individual develops a chronic disease. Genetic and environmental factors can exacerbate or attenuate oxidative stress. For example, mutations in the low-density lipoprotein receptor, a diet high in saturated fat, and a sedentary lifestyle result in hypercholesterolemia and elevated levels of oxidized cholesterol, which promote oxidative stress and associated inflammation in vascular endothelial cells and atherosclerosis (Stancu et al., 2012). In AD, mutations in the β-amyloid precursor protein (APP) or presenilin-1 result in increased production of self-aggregating oligomeric forms of amyloid β-peptide (Aβ) that induce membrane-associated oxidative stress in neurons, thereby rendering them vulnerable to dysfunction and degeneration (Mattson, 2004). In PD, mutations in α-synuclein, Parkin, or leucine-rich repeat kinase 2, or exposure to high levels of certain neurotoxins, result in mitochondrial dysfunction, oxidative stress, and the accumulation of α-synuclein in dopaminergic neurons (Moore et al., 2005). As described below, several phytochemicals have been reported to protect cells against oxidative stress in experimental models of neurodegenerative disorders.

It is commonly stated that fruits and vegetables are good for health because they contain antioxidant chemicals that directly squelch oxygen free radicals (Balsano and Alisi, 2009). Although there are such antioxidant chemicals in fruits and vegetables, humans do not

consume the prohibitively high quantities of these foods that would be required to achieve the concentrations (1–100 μmol) of such antioxidant chemicals in our cells that could scavenge major amounts of free radicals. Instead, by activating adaptive cellular stress pathways such as those described in section V below, many phytochemicals bolster intrinsic antioxidant defenses in cells, including induction of expression of antioxidant enzymes such as SOD1, SOD2, glutathione peroxidase, heme oxygenase (HO), and others as well as redox enzymes such as NAD(P)H quinone oxidoreductase 1 (NQO1) (Calabrese et al., 2010). In this view, health-promoting dietary phytochemicals are mildly noxious to cells, inducing oxidative stress and thus triggering evolutionarily conserved adaptive stress responses that result in the upregulation of proteins and peptides that detoxify ROS. In the remainder of this section, we provide examples of studies in which specific commonly consumed phytochemicals have been shown to protect cells against oxidative stress (Fig. 4), with a focus on neuroprotection.

Sulforaphane, which is present in broccoli, Brussels sprouts, and other green vegetables, can protect cultured dopaminergic neurons against oxidative insults relevant to the pathogenesis of PD, including 6-hydroxydopamine (6-OHDA) (Han et al., 2007). Sulforaphane treatment also protected dopaminergic neurons and reduced motor deficits in an in vivo mouse PD model (Morroni et al., 2013). In models relevant to stroke, sulforaphane protected cultured mouse hippocampal neurons against oxygen and glucose deprivation, and hemin; this neuroprotection was associated with increased expression of the antioxidant enzymes NQO1 and HO1 (Soane et al., 2010). Membrane-associated oxidative stress occurs in neurons in AD as a result of aggregation of Aβ. When mice were treated with sulforaphane, the adverse effects of Aβ on learning and memory were ameliorated (Kim et al., 2013a), consistent with protection against the oxidative stress caused by Aβ.

Curcumin, the key chemical in curry spice (turmeric root; *Curcuma longa*), can protect neurons against dysfunction and degeneration in a range of experimental cell culture and animal models. Curcumin protected cultured neurons against direct oxidative insults including exposure to copper (Huang et al., 2011), hydrogen peroxide (Ray et al., 2011), and *tert*-butyl hydroperoxide (Zhu et al., 2004). In vivo studies in rats and mice demonstrated that curcumin treatment ameliorates learning and memory deficits caused by exposure to arsenic (Yadav et al., 2011), Aβ (Ahmed et al., 2010), and severe epileptic seizures (Choudhary et al., 2013). In cell culture and mouse models of PD, curcumin protected dopaminergic neurons against glutathione depletion and protein oxidation (Jagatha et al., 2008). In addition to protecting neurons against oxidative stress, curcumin can stimulate the production of new neurons from neural stem cells in the dentate gyrus of the hippocampus (Kim et al., 2008), which may contribute to the enhancement of spatial learning and memory.

Flavonoids are plant secondary metabolites that include a ketone moiety in their molecular backbone. They are present in varying amounts in many different commonly consumed fruits and vegetables. Examples of some of the most widely studied flavonoids are quercetin (present in onions as well as most citrus fruits and berries), catechins (from green tea and cocoa/dark chocolate), and luteolin (in broccoli, olive oil, and

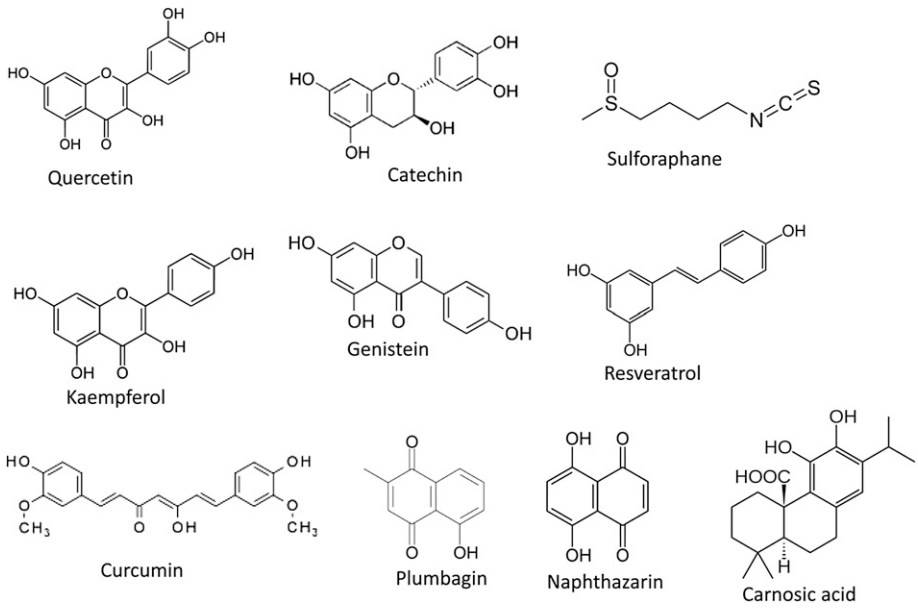

Fig. 4. Structures of phytochemicals that can activate adaptive stress response pathways. See the text for descriptions of pathways activated by these phytochemicals.

green peppers). As reviewed elsewhere, these and other flavonoids have demonstrated therapeutic effects in experimental models of cancer (Romagnolo and Selmin, 2012) and cardiovascular disease (Siasos et al., 2013). There are numerous examples of neuroprotective/therapeutic effects of flavonoids in various cell culture and animal models of neurodegenerative disorders. Treatment of cultured primary neurons with epicatechin increased their resistance to being killed by exposure to oxidized low-density lipoprotein (Schroeter et al., 2001). Treatment with epigallocatechin gallate (EGCG) reduced levels of lipid peroxidation and protein oxidation in neurons exposed to advanced glycation end products (Lee and Lee, 2007). EGCG also protected cultured spiral ganglion neurons against hydrogen peroxide (Xie et al., 2004) and cultured motor neurons against oxidative stress induced by a mutation in SOD1 that causes an inherited form of amyotrophic lateral sclerosis (ALS) (Koh et al., 2004). When cultured primary neurons were treated with relatively low concentrations of quercetin prior to exposure to Aβ1–42, their accumulation of oxidative damage (4-hydroxynonenal, protein carbonyls, and nitrotyrosine) was reduced (Ansari et al., 2009). However, consistent with a hormesis-based mechanism of action, higher concentrations of quercetin damaged the neurons. Midbrain neurons in culture were protected from apoptosis induced by hydrogen peroxide, rotenone, 1-methyl-4-phenylpyridine (MPP^+), and 6-OHDA when they were pretreated with catechin (Mercer et al., 2005). Similarly, luteolin protected cultured PC12 cells against death induced by 6-hyroxydopamine (Guo et al., 2013). Luteolin protected cultured primary rat cerebral cortical neurons from being killed by exposure to hydrogen peroxide (Zhao et al., 2011).

B. Metabolic Stress

Abnormalities in the regulation of whole-body and cellular energy metabolism are key factors in the pathogenesis of numerous major disorders, including obesity, diabetes, cardiovascular disease, and neurodegenerative disorders. Although their relative impact is much less than dietary energy restriction and exercise (Mattson, 2012), some phytochemicals can improve energy metabolism and such actions of phytochemicals may contribute to their beneficial effects on health. In keeping with a focus on the nervous system, we briefly summarize the roles of perturbed cellular energy metabolism in the pathogenesis of neurologic disorders, and then describe examples of phytochemicals that can improve neuronal bioenergetics in one or more experimental models. Analyses of glucose uptake and mitochondrial function in human patients, as well as in animal and cell culture models, suggest that vulnerable neuronal populations experience deficits in ATP and NAD^+ in AD, PD, and Huntington disease (HD) (Kapogiannis and Mattson, 2011; Exner et al., 2012; Johri et al., 2013). Genetic mutations that cause early onset inherited forms of AD (Mattson, 2004), PD (Trancikova et al., 2012), and ALS (Faes and Callewaert, 2011) compromise mitochondrial function and render neurons vulnerable to energetic stress. Ischemic stroke, a major cause of disability and death worldwide, damages and kills neurons by depriving them of glucose and oxygen.

Sulforaphane administration results in reduced brain damage in neonatal rats subjected to hypoxic/ischemic injury, a model relevant to cerebral palsy (Ping et al., 2010). When the diet of gerbils was supplemented with curcumin for 2 months and they were then subjected to transient global cerebral ischemia, death of CA1 hippocampal neurons was significantly less than in gerbils that did not receive curcumin (Wang et al., 2005a). Curcumin protected cultured neuronal cells against death induced by iodoacetate, an inhibitor of glycolysis (Reyes-Fermín et al., 2012). Curcumin treatment also reduced neuronal and microvessel degeneration in the retina in a rat model of ischemia–reperfusion injury (Wang et al., 2011c). Catechins protected cultured neurons against death induced by the mitochondrial toxin 3-nitropropionic acid (3NP) (Nath et al., 2012). Administration of luteolin to rats for 13 days beginning immediately after experimental stroke resulted in increased survival of neurons in the ischemic cerebral cortex and improved functional outcome (Zhao et al., 2011). The flavonol kaempferol protected human neuroblastoma cells and culture primary rodent neurons against apoptosis induced by the mitochondrial complex I inhibitor rotenone by a mechanism involving enhanced autophagic removal of damaged mitochondria (Filomeni et al., 2012). These findings provide evidence that neuroprotective actions of some phytochemicals involve upregulation of cellular stress resistance.

C. Proteotoxic Stress

A common theme in the pathogenesis of chronic diseases is the abnormal aggregation and accumulation of misfolded and oxidatively modified proteins inside and/or outside of cells. The protein aggregates assemble into fibrillary amyloid structures in some cases (e.g., amylin in diabetes, Aβ in AD), whereas intracellular inclusions form in other disorders (e.g., huntingtin in HD and prion proteins in prion disorders). There is increasing evidence that some phytochemicals can inhibit the production, aggregation, and/or cytotoxicity of pathogenic proteins. In this section, we illustrate the potential for phytochemicals to prevent or reverse sproteotoxic stress in models of neurodegenerative disorders.

When injected into the brain of mice or rats, aggregating Aβ damages neurons and can cause learning and memory deficits. Using the latter model of AD, treatment of mice with sulforaphane ameliorated cognitive

deficits without affecting the aggregation of Aβ (Kim et al., 2007). Overexpressed α-synuclein results in neurodegeneration in *Drosophila*, which can be prevented when the flies' food is supplemented with sulforaphane (Trinh et al., 2008). Biophysical analyses suggest that curcumin can reduce α-synuclein aggregation and toxicity, in part, by binding directly to α-synuclein (Singh et al., 2013). However, curcumin may also protect neurons against proteopathic proteins by bolstering stress resistance. For example, Wang et al. (2010b) showed that curcumin can protect human dopamine-producing neuroblastoma cells against oxidative stress and death induced by α-synuclein (Wang et al., 2010b). Similarly, curcumin attenuated mitochondrial dysfunction and oxidative stress in a culture cell model in which expression of mutant (A53T) α-synuclein is inducible (Liu et al., 2011). In an experimental model of HD, the accumulation of mutant huntingtin protein in cells was attenuated by sulforaphane treatment by a mechanism involving enhanced degradation of huntingtin in the ubiquitin proteasome pathway (Liu et al., 2014). Curcumin inhibited the formation of huntingtin aggregates by modulating an endosomal sorting pathway (Verma et al., 2012). Therefore, there are multiple mechanisms by which phytochemicals can protect neurons against the accumulation and/or adverse effects of self-aggregating neurotoxic proteins involved in AD, PD, and HD.

D. Inflammatory Stress

Although the controlled surveillance and activity of immune cells are critical for tissue homeostasis and responses to pathogens and injury, chronic inflammation contributes to the pathogenesis of numerous chronic diseases, including neurodegenerative disorders (Schwartz et al., 2013). Pathologic inflammation typically involves sustained activation of cells involved in both innate and adaptive components of immune responses. Macrophages (and microglia in the central nervous system) accumulate at the site of pathology (joints in arthritis, amyloid deposits in AD, ventral spinal cord in ALS, etc.), where they produce proinflammatory cytokines and ROS that can damage cells (Aktas et al., 2007; Ransohoff and Brown, 2012). Monocytes and T lymphocytes are also often recruited to the site of pathology, where they mediate autoimmune attack on self-antigens (Wraith and Nicholson, 2012).

Numerous phytochemicals have been reported to reduce inflammation in one or more disease models, and reviews on this topic were recently published (Leiherer et al., 2013; Madka and Rao, 2013). Mechanisms by which some phytochemicals can suppress neuroinflammation are described in section V below. Here we describe several examples of studies in which one or more phytochemicals are shown to have beneficial effects in experimental models of neurologic disorders that involve chronic inflammation.

Ten flavonoids isolated from the tree *Rhus verniciflua* were tested for their ability to protect cultured neural cells against glutamate toxicity, and four (fisetin, sulfuretin, butein, and butin) were found to bolster antioxidant defenses (glutathione peroxidase and glutathione) (Cho et al., 2012). The latter study further showed that the flavonoids also inhibit lipopolysaccharide (LPS)-induced NO production in a microglial cell line, indicating an anti-inflammatory action of the flavonoids. In a model of multiple sclerosis in which mice were injected with a myelin peptide to stimulate the immune system to "attack" myelinated axons, sulforaphane inhibited the development of disease symptoms and reduced activation of Th17 cells, a specific type of T lymphocyte implicated in the pathogenesis of multiple sclerosis (Li et al., 2013a). Similarly, when administered orally, epigallocatechin-3-gallate reduced myelin-reactive T cell proliferation and tumor necrosis factor production, and protected neurons against degeneration in a mouse model of multiple sclerosis (Aktas et al., 2004). Inflammation of cerebral vascular cells plays an important role in secondary infarction (stroke) in patients with subarachnoid hemorrhage. In a mouse model of the latter disorders, curcumin treatment reduced vascular inflammation and vasospasm (Wakade et al., 2009). Old mice often exhibit spatial working memory deficits associated with elevated levels of inflammatory cytokines and activated microglia in the hippocampus. When old mice were fed a diet supplemented with luteolin, their spatial working memory was improved and markers of inflammation in the hippocampus were reduced (Jang et al., 2010a). When APP mutant transgenic mice (a mouse model of AD) were treated with curcumin, levels of Aβ were reduced in the brain and this was associated with reduced local inflammation as indicated by reduced levels of activated microglia and interleukin-1β (Lim et al., 2001).

Although the kinds of cytoprotective actions of phytochemicals described in this section are consistent with them inducing adaptive stress responses, their mechanism of action was not established in most cases, and the authors assumed or speculated that the phytochemicals acted as direct free radical scavengers in many cases. However, as described in section V below, most if not all of these phytochemicals activate one or more adaptive stress response pathways, thereby bolstering cellular resistance to dysfunction and degeneration.

V. Phytochemicals and Organismal Stress Resistance

Organisms and their cells have evolved to maintain homeostasis in constantly changing environments with adaptive stress responses enabling survival and fitness. In the previous section, we described evidence that some phytochemicals can protect neural cells against oxidative, metabolic, proteotoxic, and inflammatory stress. In

this section, we describe effects of phytochemicals on the vulnerability of organ systems to major/catastrophic stressors with a continuing focus on the nervous system. The evidence is consistent with the hypothesis that numerous phytochemicals produced by commonly consumed plants stimulate beneficial stress responses that bolster stress resistance and enhance tissue repair. Many of these adaptive responses are similar to those occurring in response to exercise, dietary energy restriction, heat shock, and preconditioning ischemia (Mattson, 2012; Milisav et al., 2012; Longo and Mattson, 2014).

A. Ischemia: Stroke and Myocardial Infarction

Blood carries oxygen and nutrients critical for the function and viability of all tissues, which is particularly crucial in highly aerobic tissues such as heart and brain. Disruption of the blood supply, such as occurs in myocardial infarction and stroke, can cause irreversible damage to the tissue in a short time period, with cells dying by necrosis or apoptosis depending upon the intensity and duration of the ischemia they experience. Reperfusion injury involves additional oxidative damage that occurs after restoration of blood supply. The resistance of tissues to ischemic damage can be enhanced by ischemic preconditioning (IPC), a process in which an organ is exposed to a short period of moderate ischemia prior to a more severe ischemic insult. IPC can occur during the evolution of atherosclerotic heart disease or cerebrovascular disease in which repeated transient ischemic episodes protect tissues during a subsequent major ischemic event. Experimental IPC has been widely used in studies of the heart (Murry et al., 1986) and brain (Kitagawa et al., 1990). Broad ranges of studies were performed to evaluate the effects of IPC and its mechanisms. Even more mild physiologic intermittent energetic stresses, such as intermittent fasting, can protect the heart and brain against ischemic injury (Yu and Mattson, 1999). Might phytochemicals mimic some of the effects of IPC?

Epidemiologic evidence suggests that high intakes of fruits, vegetables, and polyphenol-rich foods such as cocoa and green tea are associated with a lower risk of death from coronary heart disease and stroke (Sudano et al., 2012). Several phytochemicals have been reported to protect the heart and brain against ischemic damage. The herbal plant *Scutellaria baicalensis* containing flavonoids (e.g., baicalein, baiclain, oroxylin A, and norwogonin) can induce preconditioning of the heart, thereby conferring a resistance to ischemia–reperfusion injury (Whittenburg, 1990). Naringenin, a major flavanone in grapefruit, significantly reduced myocardial infarction heart damage by a mechanism involving activation of mitochondrial potassium channels (Testai et al., 2013). Baiclein pretreatment protected chick cardiomyocytes against ischemia/reperfusion in part by activating mitochondrial KATP channels (Chang et al., 2013). Genistein, an isoflavone and phytoestrogen present in soybeans and some medicinal plants, is cardioprotective when administered at a low dose in a coronary artery occlusion-reperfusion model (Tissier et al., 2007), whereas a high dose can exacerbate ischemic damage (Imagawa et al., 1997). In addition to protecting against ischemic injury, polyphenol phytochemicals have been reported to modify the development of cardiac hypertrophy, ventricular remodeling, and fibrosis after myocardial infarction (Jiang et al., 2010).

Dietary plant polyphenols also exert neuroprotective effects and improve cognitive function in animal models of cerebral ischemia. In addition to their antioxidant, anti-inflammatory, and antiapoptotic actions, phytochemicals can stabilize mitochondrial membranes, enhance glutamate uptake, and normalize intracellular calcium levels in neurons (Panickar and Jang, 2013). On the basis of epidemiologic and experimental data, the consumption of red wine and/or grapes can protect the heart and brain against ischemic disease (Trinh et al., 2008). Studies focused on resveratrol, which is enriched in red wine and grapes, revealed neuroprotective efficacy of this phytochemical in models of ischemic stroke (Huang et al., 2001; Sinha et al., 2002; Inoue et al., 2003). Resveratrol was found to mimic IPC neuroprotection against cerebral ischemia by a mechanism involving activation of sirtuin (SIRT) 1 (Raval et al., 2006). Recent findings further suggest that resveratrol administration can reduce ischemic brain damage by protecting the endothelium of the cerebrovasculature (Clark et al., 2012).

Turmeric has traditionally been used in South Asia for the treatment of diseases associated with vascular injury and inflammation (Lodha and Bagga, 2000). Curcumin has a broad spectrum of efficacy in inflammation-related diseases. Several reports have shown that curcumin has a neuroprotective effect against cerebral ischemia in animal models, and these early studies attributed the neuroprotective effect of curcumin to its intrinsic antioxidative properties (Ghoneim et al., 2002; Thiyagarajan and Sharma, 2004; Wang et al., 2005a). However, more recent findings suggest that the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and HO1 upregulation (see section V.A.1. below) mediate curcumin's neuroprotective effect in ischemic stroke models (Yang et al., 2009a). Several reports also suggest that curcumin preserves the integrity of the blood–brain barrier under ischemic conditions (Jiang et al., 2007; Kaur and Ling, 2008; Wang et al., 2013).

Neuroprotective effects of green tea extract and its active polyphenol, (−)-EGCG, have been widely reported in ischemic brain injury models (Hong et al., 2000, 2001; Choi et al., 2004; Egashira et al., 2007). In addition, the amino acid L-theanine in the tea leaves also shows a neuroprotective effect in animal models of stroke (Park et al., 2010; Zukhurova et al., 2013). In

addition to its antioxidant properties, the neuroprotective effects of EGCG may involve matrix metalloproteinase (MMP)-9 inhibition and Nrf2/HO1 activation (Sutherland et al., 2006; Park et al., 2010; Shah et al., 2010). Epidemiologic data suggest an inverse relationship of consumption of green tea and stroke incidence in the Japanese population (Tanabe et al., 2008). Protective actions of green tea polyphenols on the cerebrovasculature were reported in the studies of blood–brain barrier permeability and microvessel fragmentation in rats with cerebral ischemia (Zhang et al., 2010b; Liu et al., 2013a).

Although individual phytochemicals can reduce brain damage and improve functional outcome in stroke models, complex mixtures of phytochemicals are consumed in diets rich in vegetables, fruits, and herbs. Future research should elucidate whether combinations of phytochemicals exhibit additive or synergistic (or antagonistic) effects on the vulnerability of organs to ischemia. In addition, future therapeutic strategies may include combinations of phytochemicals with drugs to improve efficacy and/or reduce side effects of drugs. For instance, combined treatment with memantine (an *N*-methyl-D-aspartate–type glutamate receptor blocker used to treat AD patients) and tea polyphenols was more effective than memantine or the tea polyphenols alone in protecting neurons in a mouse model of excitotoxic neurodegeneration (Chen et al., 2008). Likewise, combined treatment with curcumin and candesartan (an angiotensin II receptor antagonist used mainly for the treatment of hypertension) were synergistic in protecting against ischemic brain damage in mice (Awad, 2011).

B. Environmental Toxicants

Most organisms, including humans, are regularly exposed to chemicals that have the potential to cause damage. Such environmental toxicants include heavy metals, volatile organic chemicals in exhaust from burning of petroleum products, and human-made chemicals (e.g., polychlorinated biphenyls, dioxins, dichlorodiphenyltrichloroethane). These environmental toxicants are particularly damaging to the developing embryo as well as vulnerable populations of adults. In many cases, the brain is highly sensitive to toxicants, with exposure to lead, mercury, arsenic, pesticides, and carbon monoxide being well known examples (Grandjean and Landrigan, 2006; Williams and Ross, 2007). Indeed, the hormesis-based biphasic dose response is familiar to readers of murder mysteries such as *Arsenic and Old Lace*. Phytochemicals can themselves be toxic when ingested in high amounts; however, in many cases, those same phytochemicals can be beneficial when ingested in lower amounts, effectively protecting against a range of toxicants. Here we describe examples of studies in which administration of specific phytochemicals to animals can protect the brain against exposures to environmental toxins.

Exposure of cats to a high level of arsenic results in oxidative stress and brain damage that can be ameliorated when the cats are pretreated with resveratrol (Cheng et al., 2013). In a rat model of arsenic toxicity, quercetin treatment protected the liver and brain against oxidative damage (Ghosh et al., 2009). Curcumin treatment attenuated arsenic-induced depletion of monoamine neurotransmitters in the striatum, hippocampus, and cerebral cortex of rats (Yadav et al., 2010). Oral administration of nanoparticulate curcumin reduced arsenic-induced oxidative damage in the kidney and brain of rats (Sankar et al., 2013). Naturally occurring excitotoxins such as kainic acid and domoic acid can cause severe epileptic seizures and degeneration of hippocampal neurons (Bruce-Keller et al., 1999). Curcumin treatment protected hippocampal neurons in mice against kainic acid–induced damage (Shin et al., 2007). Several types of fungi produce a chemical called 3NP that is a potent inhibitor of mitochondrial succinate dehydrogenase. Exposure of rats and mice to 3NP causes selective degeneration of medium spiny neurons in the striatum and associated motor symptoms similar to those of patients with HD (Bruce-Keller et al., 1999). Rats treated with curcumin were relatively resistant to 3NP-induced striatal damage and exhibited preservation of mitochondrial function compared with vehicle-treated rats exposed to 3NP (Sandhir et al., 2014) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was originally identified as a contaminant of heroin that was responsible for the rapid development of PD-like symptoms in several young drug users. MPTP causes a highly selective degeneration of dopaminergic neurons in the substantia nigra of mice and monkeys and has therefore been widely used to model PD in these animals (Duan and Mattson, 1999; Maswood et al., 2004) Treatment of mice with curcumin protected dopaminergic neurons against MPTP-induced degeneration by a mechanism involving reduced inflammation (Ojha et al., 2012). Sulforaphane administration also protected mice against MPTP-induced degeneration of substantia nigra dopaminergic neurons, and suppressed gliosis and inflammation (Jazwa et al., 2011). Similarly, theaflavin treatment attenuated dopamine depletion and ameliorated behavioral deficits in MPTP-treated mice (Anandhan et al., 2012).

Endocrine-disrupting chemicals (EDCs) have posed a growing concern for human health. The US Environmental Protection Agency has defined EDCs as agents that interfere with the synthesis, secretion, transport, metabolism, binding actions, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and development processes. These substances have been shown to adversely affect the reproductive and nervous systems (Diamanti-Kandarakis et al., 2009). Animal studies have shown that EDCs such as bisphenol

A (BPA) and phthalates, key ingredients in modern plastics, can disrupt the delicate endocrine system, leading to altered cognitive developmental and behavioral problems in the nervous system (Schantz and Widholm, 2001; Dessì-Fulgheri et al., 2002; Laviola et al., 2005; Xu et al., 2012; Jurewicz et al., 2013). These EDCs were designed to be less sensitive to the decay and degradation that reduce the amount of the chemicals released from the plastics on the one hand, but keep them present in the environment on the other hand. It remains to be established whether the levels of BPA to which humans are being exposed are causing health problems. However, a recent study showed that environmental exposure to BPA was associated with maladaptive behavior and learning problems in school-aged children (Hong et al., 2013).

There are several natural chemicals found in soybean products that can act as EDCs in laboratory animals, including coumestans, phenylflavonoids, and isoflavones such as genistein. Such phytoestrogens provide a prominent example of phytochemicals that have beneficial effects at low concentrations but adverse effects at higher concentrations. Thus, low amounts of phytoestrogens can protect against various cancers such as prostate, breast, bowel, and other cancers (Adlercreutz, 2002; Zhao and Mu, 2011). Moreover, soy isoflavones, including genistein and daidzein, can protect neurons in animal models of ALS, stroke, chronic sciatic nerve injury, and PD (Trieu and Uckun, 1999; Liu et al., 2008; Valsecchi et al., 2008; Chinta et al., 2013). Interestingly, findings suggest that soy isoflavones can improve cognitive function in postmenopausal women (Kritz-Silverstein et al., 2003). These beneficial effects of soy isoflavone might be mediated by estrogen receptor (ER)–mediated processes. However, at higher concentrations, genistein inhibits tyrosine kinases (Akiyama et al., 1987), some of which are involved in long-term potentiation and cognitive function. Studies of the effects of soy isoflavones on cognitive function in men are as yet inconclusive (Lund et al., 2001; Lee et al., 2004). Therefore, it can be postulated that soy phytoestrogens may enhance cognitive function at low doses, but impair cognitive function when ingested in higher amounts. The amounts of diet-derived phytoestrogens typically consumed may be below the concentration range that inhibits tyrosine kinases (Lee et al., 2005). Similar to genistein, biphasic effects of curcumin on the nervous system have also been reported (Wang et al., 2010b; Singh et al., 2013), including a biphasic dose-response effect on hippocampal neurogenesis in mice (Kim et al., 2011a).

C. Psychologic Stress

Stress can be defined broadly as a psychologic and physical response of the body that occurs whenever an individual has to adapt to changing conditions. It is well known that chronic uncontrolled psychologic stress is detrimental for overall health and mental health in particular (Kessler, 1997; Hammen, 2005). Psychologic stress occurs when an individual perceives that environmental demands tax or exceed his or her adaptive capacity (Cohen et al., 2007). However, mild stress may be desired, beneficial, and protective, as is clear from the many health benefits of exercise and fasting (Mattson, 2012; Longo and Mattson, 2014). Extract of the *Hypericum perforatum* plant (St. John's wort) is a herbal treatment for depression (Nahrstedt and Butterweck, 2010), with some studies suggesting an efficacy similar to or greater than the widely prescribed antidepressant fluoxetine (Fava et al., 2005). The major components of St. John's wort (quercetin, hyperforin, and hypericin) may inhibit serotonin reuptake, as does fluoxetine (Singer et al., 1999; Butterweck, 2003). Other phytochemicals reported to have antidepressant effects in animal models include curcumin (Lopresti et al., 2012; Hurley et al., 2013) and resveratrol (Xu et al., 2010b). Interestingly, a large longitudinal study showed that caffeinated coffee consumption is associated with a reduced risk of depression (Lucas et al., 2011). It was also reported that ingestion of green tea has a preventative effect on the development of depression in mice and humans (Liu et al., 2013b; Zhang et al., 2013). Therefore, there is considerable evidence that some dietary phytochemicals protect the brain against stress.

Orally administered anthocyanins were reported to protect dopaminergic neurons against oxidative stress caused by psychologic or emotional distress (Rahman et al., 2008). Green tea polyphenols can also attenuate the cognitive dysfunctions induced by psychologic stress (Chen et al., 2009d). Ferulic acid (4-hydroxy-3-methoxycinnamic acid), a phenolic phytochemical in extracts of medicinal plants, spices, chocolate, and coffee, has an antidepressant-like effect in the tail suspension test through the activation of neurotrophic and neurogenic signaling pathways (Zeni et al., 2012).

Adult hippocampal neurogenesis is negatively associated with depression and anxiety, and both exercise and antidepressant drugs stimulate neurogenesis, in part by increasing the production of brain-derived neurotrophic factor (BDNF) (Castrén, 2004; Warner-Schmidt and Duman, 2006). Several studies reported that dietary phytochemicals affect adult hippocampal neurogenesis, suggesting a potential role in treating depression and anxiety disorders (Park and Lee, 2011; Dias et al., 2012). A diet enriched in polyphenols and polyunsaturated fatty acids induces neurogenesis in the hippocampus of adult mice (Valente et al., 2009). The flavone baicalein, derived from the root of *S. baicalensis*, enhances hippocampal neurogenesis in adult rats and mice (Oh et al., 2013; Zhuang et al., 2013). Similarly, the green tea polyphenol EGCG stimulates the proliferation of neural progenitor cells and enhances adult hippocampal neurogenesis by a

mechanism involving the sonic hedgehog (Shh) signaling pathway (Yoo et al., 2010; Wang et al., 2012d). Epicatechin also increases the number of dendritic spines and stimulates angiogenesis in the hippocampus, and improves learning and memory performance in mice (van Praag et al., 2007). Curcumin can also stimulate neurogenesis (Kim et al., 2008), albeit with a biphasic dose response in which high concentrations inhibit neurogenesis (Park and Lee, 2011). Whether stimulation of neurogenesis by phytochemicals is a manifestation of a stress response remains to be established.

Depression has been linked to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and some antidepressants may act in part by normalizing HPA axis function (Pariante, 2003). Similar to antidepressant drugs, phytochemicals can block or reverse the stress-induced changes typical of HPA axis dysfunction. For example, curcumin stimulated BDNF and phosphorylated cAMP response element-binding protein (CREB) signaling in the hippocampus, suggesting an antidepressant therapeutic potential of this phytochemical (Xu et al., 2006b). Interestingly, a flavonoid derivative containing 7,8-dihdyroxyflavone activates the BDNF receptor TrkB and has been shown to have therapeutic efficacy in an animal model, suggesting a potential for such neurotrophic phytochemicals in some neurologic disorders (Liu et al., 2012b).

D. Aging

Aging can be defined as the progressive changes in the structure and function of an organism that do not result from disease or other gross accidents and that eventually lead to the increased probability of death. Aging of unicellular or multicellular eukaryotic organisms is a highly complex biologic phenomenon that has led to numerous theories of aging, none of which alone explain why aging occurs. Thus, aging is a multifactorial process influenced by both genetic and environmental factors (Yu and Chung, 2006).

Aging is an evolved characteristic or adaptation that developed through the process of evolution in the same manner as any structural or functional characteristic of an animal (Goldsmith, 2008). Aerobic life evolved through adaptive processes for survival in an oxygen environment, which lead to the free radical theory of aging (Liu et al., 2011). In this respect, aging is closely related with elevated oxidative stress; thus, the hypothesis that the antioxidant and/or radical-scavenging properties of phytochemicals can endow them with "antiaging" properties was not unreasonable (González-Vallinas et al., 2013; Park et al., 2014). In addition, since Franceschi et al. (2000) first postulated that increased proinflammatory status is a driving force in the aging process, considerable evidence supports cross-amplifying effects of oxidative stress and chronic inflammation in aging and age-related diseases (Chung et al., 2009; Cevenini et al., 2010; Singh and Newman, 2011). Phytochemicals, particularly flavonoids and terpenoids, can attenuate the inflammation and oxidative stress induced by nuclear factor-κB (NF-κB) signaling in cells of the innate immune system. Epidemiologic evidence indicates that the Mediterranean diet enriched with polyphenols from regular consumption of fruits, vegetables, and red wine can inhibit inflammatory responses and attenuate many chronic age-associated diseases, including cancer as well as cardiovascular and inflammatory disorders (Liu, 2003; Pérez-Martínez et al., 2011; Singh and Newman, 2011).

Phenolic components of berries responsible for their color and flavor likely evolved in part to protect the plants against infections, physical damage, UV radiation, and other damaging factors (Paredes-López et al., 2010). Whole apple extracts can increase the lifespan of *Caenorhabditis elegans* in a dose-dependent manner, and improve the healthspan of the worms as indicated by increased mobility at older ages (Vayndorf et al., 2013). Açai palm fruit (*Euterpe oleracea* Mart.) was reported to antagonize the detrimental effect of a high-fat diet and oxidative stress on aging (Sun et al., 2010). The antiaging effects of the four dietary plant polyphenols tannic acid, gallic acid, ellagic acid, and catechin were tested in *C. elegans*, and lifespan assays showed that all four compounds prolonged lifespan, but only tannic acid and catechin protected against specific stressors (Saul et al., 2011). An oregano-cranberry mixture was shown to have a prolongevity effect in the Mexican fruit fly (Mexfly) (Zou et al., 2010, 2012a). Cocoa supplementation increases the lifespan of the fruit fly *Drosophila melanogaster* under oxidative stress conditions (Bahadorani and Hilliker, 2008). Curcumin-induced lifespan extension was reported in *Drosophila* and *C. elegans*, but not in mouse models (Suckow and Suckow, 2006; Liao et al., 2011; Shen et al., 2013a,b).

Relatively few studies have reported extension of lifespan by phytochemical treatment in rodent models. Long-term consumption of EGCG increased the average life span without affecting the maximum life span, and resulted in lower levels of age-related deterioration of the kidneys and liver in Wistar rats (Niu et al., 2013). Rapamycin, a chemical originally isolated from bacteria in a soil sample from Easter Island, is an inhibitor of the mammalian target of rapamycin (mTOR). Rapamycin extended lifespan in genetically heterogeneous mice and normal inbred 129/Sv mice (Anisimov et al., 2011; Miller et al., 2011). Although resveratrol can extend the life span of various invertebrates including, *Saccharomyces cerevisiae*, *C. elegans*, and *D. melanogaster*, resveratrol failed to increase overall survival or maximum life span in mice in the context of the standard diet (Pearson et al., 2008; Miller et al., 2011). An interesting study by Aires et al. (2012) investigated the potentiation of dietary restriction–induced life span extension by polyphenols. In the latter study, polyphenols from

blueberry, pomegranate, and green tea extracts further extended the lifespan of intermittently fed mice and reduced inflammatory markers (Aires et al., 2012).

Dietary supplements of fruit and vegetable extracts were shown to retard age-related declines in neuronal and cognitive function. Extracts from strawberry, spinach, and blueberry slowed and reversed age-related declines in cognitive and motor function in Fischer 344 rats (Joseph et al., 1998, 1999). In addition, increasing evidence suggests that dietary phytochemicals are also associated with reduced risk of disorders such as AD and PD (Son et al., 2008; Perry and Howes, 2011). Coffee and green tea polyphenols exhibited beneficial effects in treating age-related depression and cognitive decline, suggesting a potential therapeutic role of such phytochemicals in brain aging (Liu et al., 2014). Coffee has positive effects on cognition and psychomotor behavior during aging, which may involve both caffeine-mediated and caffeine-independent mechanisms (Chen et al., 2009d). The abilities of polyphenolics such as curcumin, resveratrol, and proanthocyanidins to enhance cognitive function in animal models was previously reviewed (Ogle et al., 2013).

VI. Molecular Mechanisms

Two major mechanisms by which phytochemicals exert beneficial effects on the nervous system include stimulating one or more adaptive cellular stress response signaling pathways, as well as inducing the expression of neurotrophic factors. In this section, we focus on the major molecular pathways by which phytochemicals are currently known to promote neural stress resistance and plasticity.

A. Adaptive Stress Responses

More than 50 years ago, Milkman (1962) reported that exposure of developing *Drosophila* to heat shock can protect them against more severe stress. This led to the discovery of heat shock proteins (Hsps) and related protein chaperones that help prevent the accumulation of misfolded/damaged proteins in cells subjected not only to heat stress but also to oxidative and metabolic stress (Naidoo, 2009; Doyle et al., 2013). Since then, it has become clear that cells possess a broad range of mechanisms that protect them against stressful conditions they encounter in the normal course of their lives, as well as more severe conditions that include tissue injury, diseases, and exposure to toxins. Here we highlight several such adaptive stress response mechanisms that can be triggered by phytochemicals and may mediate health-promoting actions of some vegetables and fruits.

1. Nuclear Factor Erythroid 2-Related Factor 2 Activation. Oxidants and electrophiles are ubiquitous and constantly generated in aerobic organisms where they arise from ongoing metabolism and xenobiotic challenges (Kensler et al., 2007; Ma and He, 2012; Ma, 2013). Accordingly, cells have evolved internal defense mechanisms to cope with oxidative and electrophilic stress. Nrf2 belongs to the Cap'n'Collar subfamily of basic leucine zipper transcription factors (Moi et al., 1994), and is a master regulator of cellular adaptation to redox stress. Under basal conditions, Nrf2 is kept transcriptionally inactive because it resides in cytoplasm. In response to oxidative and electrophilic stress, Nrf2 is stabilized and translocates into the nucleus, where it binds to the *cis*-acting enhancer antioxidant response element sequence (consensus core sequence: 5′-TGACnnnGC-3′) (Fig. 5). Nrf2 heterodimerizes with members of the small musculoaponeuotic fibrosarcoma oncogene family of proteins, binds antioxidant response element sequences, and thereby induces detoxifying proteins, antioxidant enzymes, and proteins involved in ubiquitin-mediated proteolysis pathways (Ma, 2013; Shelton and Jaiswal, 2013). Accordingly, Nrf2 knockout mice exhibit increased vulnerability to oxidative stress and toxins (Motohashi and Yamamoto, 2004; Kensler et al., 2007; Ma and He, 2012; Ma, 2013). Activation of the Nrf2 signaling with phytochemicals such as sulforaphane can protect animals against oxidative stress (Talalay et al., 2003).

When levels of oxidative stress are low, Nrf2 is maintained in an inactive form in the cytoplasm as the result of binding to the cysteine-rich protein Kelch-like ECH-associated protein 1 (Keap1). Keap1 is tethered to the actin cytoskeleton in the cytosol, where it binds Nrf2 and serves as an adaptor to bring Nrf2 into the Cullin (Cul) 3–based E3 ubiquitin ligase complex (Itoh et al., 1999; Dhakshinamoorthy and Jaiswal, 2001; Kang et al., 2004). In addition to keeping Nrf2 in the cytoplasm, Keap1 facilitates ubiquitin-mediated proteolysis of Nrf2 (Cullinan et al., 2004; Kobayashi et al., 2004; Zhang et al., 2004a; Furukawa and Xiong, 2005). Keap1 is a molecular sensor of ROS and genotoxic chemicals that react with specific cysteine residues in Keap1 (Cys151, Cys273, Cys288, or Cys613), which triggers a conformational change in the Nrf2/Keap1/Cul3-based E3 complex that releases Nrf2 that then translocates to the nucleus (Eggler et al., 2005; Kobayashi et al., 2006; Tong et al., 2006). Thus, knockdown or knockout of Keap1 results in constitutive activation of Nrf2 (Itoh et al., 1999; Wakabayashi et al., 2003). The subcellular localization of Nrf2 is further regulated by its nuclear localization signal sequence and nuclear export signal sequence (Jain et al., 2005; Li et al., 2005b, 2006; Theodore et al., 2008). Oxidative conditions can inactivate the Nrf2 nuclear export by modification of a redox-sensitive cysteine, which promotes the nuclear retention of Nrf2 (Li et al., 2006).

Genes induced by Nrf2 encode proteins of two major categories: antioxidant enzymes and phase 2 detoxification enzymes (Joshi and Johnson, 2012). The antioxidant

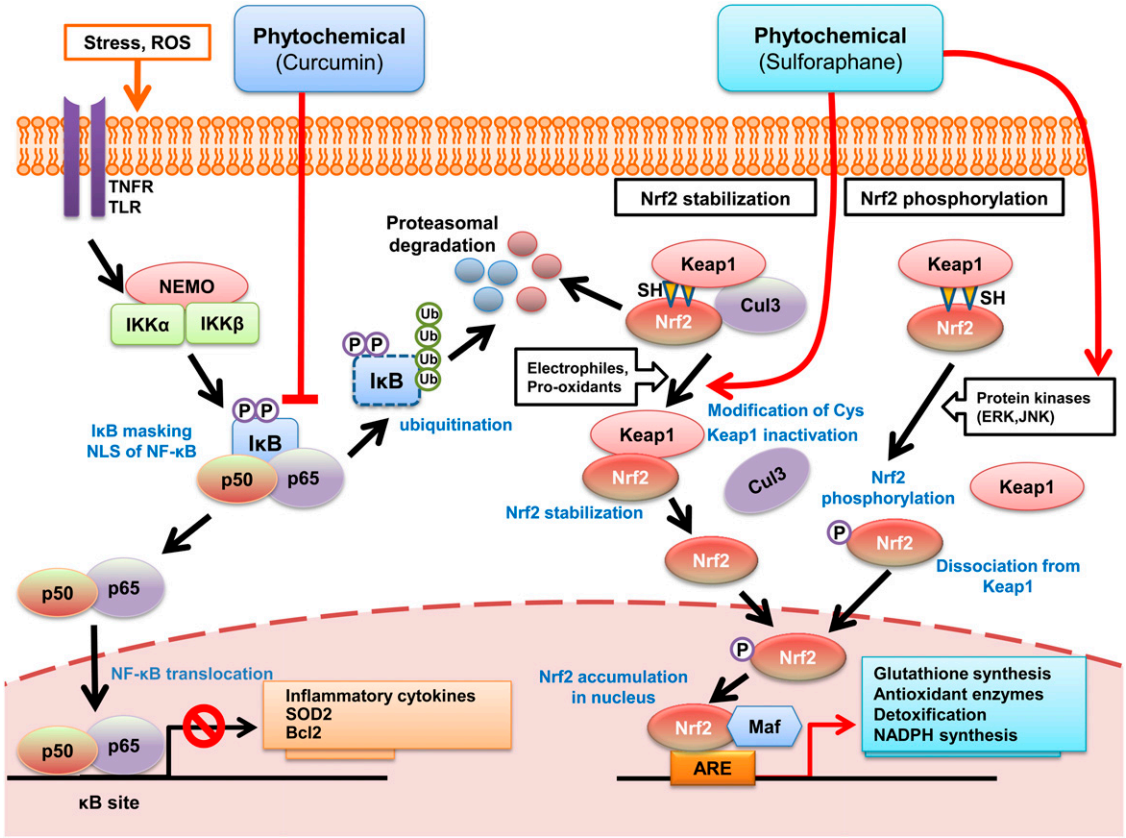

Fig. 5. Modification of the Nrf-2 and NF-κB signaling pathways by phytochemicals upregulates antioxidant and detoxification enzymes and suppresses inflammation. The Nrf2 pathway can be activated by the phytochemical sulforaphane in at least two ways, one involving interaction of sulforaphane with the SHs between Keap1 and Nrf2, and the other involving phosphorylation of Nrf2. Once freed from Keap1, Nrf2 translocates into the nucleus, where it induces the expression of genes encoding proteins involved in glutathione synthesis, antioxidant enzymes, phase 2 detoxification enzymes, and proteins involved in NADPH synthesis. Oxidative stress and ligands for TNFRs and TLRs activate upstream IKKs, resulting in phosphorylation of IκB that is normally bound to the inactive NF-κB dimer (p50 and p65) in the cytoplasm. IκB is then targeted for proteasomal degradation and NF-κB then moves into the nucleus, where it induces the expression of inflammatory cytokines as well as genes encoding proteins such as SOD2 and Bcl2 involved in adaptive stress responses. Curcumin can inhibit NF-κB in inflammatory immune cells, whereas other phytochemicals may activate NF-κB in some cell types (e.g., neurons) to enhance stress resistance. ARE, antioxidant response element; IKK, Iκ-B kinase; Maf, musculoaponeurotic fibrosarcoma oncogene homolog; NEMO, NF-κB essential modulator; NLS, nuclear localization signal; TLR, Toll-like receptor; TNFR, tumor necrosis factor receptor; Ub, ubiquitin.

enzymes include HO1, NQO1, catalase, glutathione peroxidase, thioredoxin, and peroxiredoxin. Phase 2 enzymes induced by Nrf2 include glutathione S-transferases, which catalyze the conjugation of xenobiotic electrophiles and reactive alkenals to glutathione; the conjugates are then exported from cells by multidrug resistant protein 1.

Emerging findings suggest that Nrf2 activation is one mechanism whereby phytochemicals may exert cytoprotective effects on neurons (Table 1). Examples of phytochemicals demonstrated to activate Nrf2 and upregulate Nrf2 target genes include sulforaphane, curcumin, ferulic acid, oleanolic acid, ursolic acid, the triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid, and plumbagin. In addition, well known toxic agents can activate Nrf2 even at low concentrations that induce hormetic responses. Examples include NO, dopamine, peroxides, 4-hydroxynonenal, acrolein, arsenic, and paraquat (Dinkova-Kostova et al., 2004; Ma and He, 2012; Ma, 2013; Turpaev, 2013). Nrf2 activators have few common structural properties, but most or all of them react with thiols of Keap1 (Dinkova-Kostova et al., 2001). Many of these Nrf2 activators have been shown to be effective in experimental carcinogenesis models, and their chemopreventive actions are abolished in Nrf2-deficient mice, indicating that their effects are mediated by Nrf2 (Ramos-Gomez et al., 2001; Shen et al., 2006; Xu et al., 2006a; Yates et al., 2006). Several pharmacological and genetic studies have also demonstrated neuroprotective effects of Nrf2-activating phytochemicals in animal models of AD, PD, HD, and ALS (Burton et al., 2006; Jakel et al., 2007; Kraft et al., 2007; Kanninen et al., 2008, 2009; Vargas et al., 2008; Chen et al., 2009c; Dumont et al., 2009; Yang et al., 2009b).

2. Hypoxia-Inducible Factor 1. Hypoxia can lead to rapid adaptive changes in cells, and the transcription factor hypoxia-inducible factor (HIF)-1 plays critical roles in such responses to hypoxia. HIF-1 was originally identified as a transcriptional activator of the

TABLE 1
Phytochemicals that activate the Nrf2 signaling pathway

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
Carnosol	Rat pheochromocytoma PC12 cells	Attenuate oxidative stress	Activation of Nrf2/ARE signaling	Martin et al. (2004)
Curcumin	Vascular smooth muscle cells	Inhibition of cell growth	Translocation of Nrf2 into the nucleus	Pae et al. (2007)
EGCG	Endothelial cells	Reduce oxidative stress	Upregulation of Nrf2 in the nucleus	Wu et al. (2006)
Hydroxytyrosol	Human retinal pigment epithelial cells	Block mitochondrial dysfunction and apoptosis	Nrf2 activation	Zou et al. (2012b)
Mollugin	Human oral squamous carcinoma cells	Cell growth inhibition and apoptosis	Activation of Nrf2	Lee et al. (2013)
	Mouse hippocampal HT22 cells and microglial BV cells	Suppression of cell death and inflammation	Nuclear accumulation of Nrf2	Jeong et al. (2011)
Phytochemical-rich diets	Hypertensive rats	Reduce heart failure progression	Increased cardiac Nrf2 activity	Seymour et al. (2013)
Phytochemical combination	HL-1 cardiomyocytes	Increase antioxidant defenses and protect heart cells	Induced Nrf2 activation and phase II enzymes	Reuland et al. (2013)
	Human liver hepatoma cells	Cancer chemopreventive activity	Enhanced Nrf2/ARE pathway	Saw et al. (2011)
Procyanidin	HepG2 human hepatocarcinoma cells	Anticarcinogenic effect	Induction of Nrf2/ARE pathway	Bak et al. (2012b)
Resveratrol	Human erythroleukemia K562 cells	Induce detoxification reactions by activation of Nrf2/ARE/NQO1	Phosphorylation of Nrf2	Hsieh et al. (2006)
Silymarin	Human A549 adenocarcinoma cells	Reduce paraquat-induced toxicity	Induction of Nrf2	Podder et al. (2012)
Sulforaphane	Rat lymphocytes	Chemoprevention	Increased Nrf2 and target genes	Wang et al. (2012b)
	Rat cardiomyocytes	Cardiac cell survival	Nrf2 phosphorylation	Leoncini et al. (2011)
	COPD	Restore bacteria recognition and phagocytosis	Activation of Nrf2	Harvey et al. (2011)
	Human bladder cells and tissue	Inhibit carcinogen-induced DNA damage	Activation of Nrf2	Ding et al. (2010)

ARE, antioxidant response element; COPD, chronic obstructive pulmonary disease.

erythropoietin gene in hepatoma cells (Semenza and Wang, 1992). It is expressed widely in mammalian cells, and is evolutionarily conserved (Wang and Semenza, 1993b; Firth et al., 1994; Loenarz et al., 2011; Ratcliffe, 2013). HIF-1 is related to the family of basic-helix-loop-helix transcription factors, which are responsible for cellular and tissue adaptation to low oxygen tension. HIF-1 is composed of two subunits, an oxygen-regulated α subunit (HIFα), and a constitutively expressed aryl hydrocarbon nuclear translocator also named HIF-1β (Maxwell, 2004; Metzen and Ratcliffe, 2004). These isoforms interact with histone acetyltransferases, such as CREB-binding protein (CBP), p300, and SRC-1 to activate the transcription of target genes (Wang et al., 1995a; Gu et al., 1998; Wenger, 2002; Maynard et al., 2003). The basic-helix-loop-helix and Per-Arnt-Sim domains are required for dimerization of HIF-1α with HIF-1β as well as for binding to hypoxia-response elements comprising a consensus sequence 5′-RCGTG-3′ within or near HIF-1 regulated genes. In addition to the binding to DNA and coactivators, HIF-1α interacts with factors regulating its stability such as Hsp90 (Brahimi-Horn et al., 2005; Fandrey et al., 2006). Transcription and translation of HIF-1α occurs constitutively, but the stability and activity of this protein is dependent on oxygen levels, whereas HIF-1β expression and the protein stability are independent of oxygen levels (Wang and Semenza, 1995; Kallio et al., 1998). HIF-1 regulates an array of genes that participate in angiogenesis, iron and glucose metabolism, cell proliferation, and cell survival (Shi, 2009; Singh et al., 2012).

Under normoxic conditions (normal oxygen tension), HIF-1α is hydroxylated on at least one of two conserved proline residues (either P403 or P564 in human HIF-1α) within the oxygen-dependent degradation domain by specific prolyl hydroxylases (PHDs) (Ivan et al., 2001; Jaakkola et al., 2001; Masson et al., 2001; Koh and Powis, 2012). Functional activity of PHDs requires the cofactors iron (Fe^{2+}) and ascorbate as well as the cosubstrates oxygen (O_2) and 2-oxoglutarate (Corcoran and O'Connor, 2013). Oxygen-dependent prolyl hydroxylation of HIF-1α enables binding of the β-domain of von Hippel-Lindau tumor suppressor protein (pVHL), the recognition subunit of an E3 ubiquitin ligase complex (Elongin BC/Cul2/pVHL) that ubiquitinates HIF-1α and thereby targets it for degradation in the 26S proteasome (Kaelin and Ratcliffe, 2008). In hypoxic conditions, prolyl hydroxylation of HIF-1α and its consequent recognition by the pVHL ubiquitin–ligase complex are abrogated, and HIF-1α proteins accumulate in the nucleus where they dimerize with the constitutively expressed

HIF-1β subunit (Kaelin and Ratcliffe, 2008). In addition to oxygen, the stability of HIF-1α is also regulated by metabolic status because the tricarboxylic acid cycle intermediate α-ketoglutarate is also a substrate for PHDs. These hydroxylases insert one oxygen atom into a proline residue, and the other oxygen atom is inserted into α-ketoglutarate to generate CO_2 and succinate (Semenza, 2013). Several tricarboxylic acid cycle intermediates such as succinate and fumarate, as well as ROS such as NO, can impair PHD activity leading to stabilization and activation of HIF-1α (Selak et al., 2005; Kaelin and Ratcliffe, 2008). This aberrant stabilization of HIF-1α independent of the oxygen tension is termed *pseudohypoxia*. Pseudohypoxia-mediated HIF activity may be a cause of tumors associated with the mutations in *VHL* and tricarboxylic acid cycle enzymes (Semenza, 2013).

Systemic hypoxia quickly increases the nuclear level of HIF-1α protein in brain cells (Stroka et al., 2001; Bernaudin et al., 2002). HIF-1 responds to reduced oxygen tension in cerebral ischemia (Stroka et al., 2001; Singh et al., 2012). Both detrimental and neuroprotective roles of HIF-1 have been reported in ischemic stroke models (Helton et al., 2005; Baranova et al., 2007; Chen et al., 2007; Shi et al., 2009; Xin et al., 2011). Neuron-specific deficiency of HIF-1α increases brain injury and mortality in a mouse model of transient focal cerebral ischemia, implicating a neuroprotective function of HIF-1α (Baranova et al., 2007). Moreover, hypoxic preconditioning induces stroke tolerance in mice via HIF-1α signaling (Liu et al., 2005; Wacker et al., 2012). Other studies, however, show that deletion or inhibition of HIF-1α resulted in reduced brain damage after ischemic stroke or hypoxic conditions, suggesting a detrimental role of HIF-1α (Helton et al., 2005; Chen et al., 2009a; Cheng et al., 2014).

The HIF signaling cascade is regulated transcriptionally by NF-κB and post-translationally by PHDs (van Uden et al., 2008). Stabilized HIF-1 increases several genes to promote cell survival in low-oxygen conditions including glycolysis enzymes, which allow ATP synthesis in an oxygen-independent manner, and vascular endothelial growth factor, which promotes angiogenesis (Lee et al., 2007). A naturally occurring estrogen metabolite 2-methoxyestradiol was shown to inhibit tumor growth and angiogenesis by disrupting microtubules, HIF-1α translation, and its nuclear translation (Mabjeesh et al., 2003a). The interaction between Hsp90 and HIF-1α is required for HIF-1α stabilization (Gradin et al., 1996). The *Streptomyces hygroscopicus* metabolite geldanamycin binds to the ATP/ADP binding pocket of Hsp90, resulting in inhibition of HIF-1 activation by promoting pVHL-independent proteasomal degradation of HIF-1α protein (Isaacs et al., 2002). The plant isoflavone genistein inhibits HIF-1 by blocking the induction of HIF-1α protein (Wang et al., 1995b). Various HIF-1 inhibitors have been identified from natural product libraries and activity-guided fractionation using plants and marine organisms, including sodwanone and yardenone triterpenes from the marine sponge *Axinella*, manassantin B and 4-*O*-demethylmanassantin B from *Saururus cernuus*, laurenditerpenol from the marine alga *Laurencia intricate*, and terpenoid tetrahydroidoquinoline alkaloids emetine, klugine, and isocephaeline (Xia et al., 2012). Manassantin-type dineolignans (manassantin B and 4-*O*-demethylmanassantin B) are among the most potent small molecule HIF-1 inhibitors discovered (IC_{50} values of 3–30 nM), and selectively inhibit the activation of HIF-1 by hypoxia (Hodges et al., 2004). However, systemic administration of HIF-1 inhibitors for cancer therapy is contraindicated in patients who also have ischemic cardiovascular or cerebrovascular diseases, in which HIF-1 activity is protective (Semenza, 2012).

Phytochemicals may affect HIF-1 activity by oxygen level–independent mechanisms including generation of ROS (Prabhakar and Semenza, 2012). HIF-1 has been proposed to mediate the adaptive stress responses and beneficial mechanisms of several phytochemicals in the regulation of metabolism and stress resistance. HIF-1 activating agents may be able to prevent ischemia/reperfusion injuries and help recovery from tissue ischemia (Nagle and Zhou, 2006). In addition, some preconditioning strategies that induce HIF-1 have been applied for myocardial infarction and for ischemic rescue in the brain (Rodríguez-Jiménez and Moreno-Manzano, 2012). The iron chelator, deferoxamine, is the first natural product shown to activate HIF-1 (Wang and Semenza, 1993a); chelation of iron by deferoxamine stabilizes HIF-1α by disrupting the hydroxylation of HIF-1α by inhibition of PHD (Dendorfer et al., 2005). The β-diketone dibenzoylmethane found in licorice (*Glycyrrhiza glabra*) stabilizes HIF-1α protein and increases expression of vascular endothelial growth factor (Mabjeesh et al., 2003b). The flavonoid quercetin activates HIF-1α by inhibition of factor-inhibiting HIF, an asparaginyl hydroxylase that modifies and inactivates HIF-1α protein (Welford et al., 2003). Green tea catechin EGCG increases the level of nuclear HIF-1α protein and activates the expression of HIF-1 downstream genes (Zhou et al., 2004). The structurally related fungal sesquiterpenes pycnidione, epolone A, and epolone B induce erythropoietin expression via HIF-1α activation (Cai et al., 1998; Wanner et al., 2000). In a study of cultured dorsal root ganglia, it was found that neuronal NO induces the HIF-1–dependent expression of erythropoietin in adjacent Schwann cells, and the erythropoietin in turn protects axons of the neurons against neurotoxin-induced degeneration (Keswani et al., 2011). In contrast with the Nrf2 stress response pathway, far fewer studies have investigated the effects of phytochemicals on the HIF-1 pathway (Table 2). It will be of considerable interest to identify phytochemicals that affect the latter pathway

TABLE 2
Phytochemicals that modify the HIF-1α signaling pathway

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
EGCG	Nonsmall cell lung cancer cells and A549 xenografted tumors of nude mice	Inhibit angiogenesis	Inhibition of HIF-1α	He et al. (2013)
	Human pancreatic carcinoma cells	Inhibit cell proliferation	Inhibition of HIF-1α	Zhu et al. (2012)
	Rat kidney	Block iron uptake	Prevented HIF-1α hydroxylation by prolyl hydroxylase inhibition	Manalo et al. (2011)
3,3′-diindolylmethane	Hypoxic tumor cells	Interact mitochondrial F_1 F_0-ATPase and increased ROS and O_2	Reduced HIF-1α	Riby et al. (2008)
Ferulic acid	HUVECs	Augment angiogenesis	Upregulation of HIF-1α	Lin et al. (2010)
Honokiol	HUVECs	Promote angiogenesis	Inhibition of HIF pathway	Vavilala et al. (2012)
Luteolin	Human retinal microvascular endothelial cells	Inhibit retinal neovascularization	Suppressed HIF-1α expression	Park et al. (2012b)
Naringenin and quercetin	Hypoxia-induced mice model	Ameliorate hypoxia-induced brain dysfunction	Decreased HIF-1α	Sarkar et al. (2012)
Salvia miltiorrhiza	Human gastric cancer cells and human hepatocarcinoma cells	Anticancer activity	Suppressed HIF-1α accumulation	Dat et al. (2007)
Silibinin	SKH1 hairless mice	Prevent UVB-induced photocarcinogenesis	Decreased HIF-1α	Gu et al. (2007)
	Ischemic stroke model	Reduce infarct volume and brain edema	Upregulation of HIF-1α	Wang et al. (2012a)
Soy-containing diets	Acute stroke in female rats	Decrease the expression of apoptotic mediator	Inhibition of HIF-1α activity	Ma et al. (2013)
Quercetin	Human breast cancer cells	Inhibit cell proliferation and invasion	Suppressed the expression of HIF-1α	Li et al. (2013b)
	Gastric cancer cells	Induce apoptotic cell death	Modulation of HIF-1α	Wang et al. (2011b)
Wogonin	Acute UVB-irradiated hairless mice	Reduce skin damage	Inhibition of HIF-1α	Kimura and Sumiyoshi (2011)

HUVEC, human umbilical vein endothelial cell.

and the potential interactions of Nrf2 and HIF-1 pathways in cellular responses to individual phytochemicals and to combinations of phytochemicals normally present in plants.

3. Nuclear Factor-κB. NF-κB is a protein complex that regulates the expression of genes involved in a range of biologic processes including innate and adaptive immunity, inflammation, cellular stress responses, cell survival, and proliferation. NF-κB is ubiquitously expressed in almost all animal cell types, where it is located in the cytoplasm in an inactive form bound to an inhibitory protein (IκB) that masks the nuclear localization signal of the NF-κB transcription factor dimer (typically p65 and p50 subunits) (Jacobs and Harrison, 1998). In response to stimuli including inflammatory cytokines, ionizing radiation, or bacterial or viral antigens, IκB is phosphorylated by the IκB kinase complex and is ubiquitinated and degraded by the proteasome, allowing NF-κB to translocate into the nucleus and regulate gene expression (Karin, 1999; Mankan et al., 2009) (Fig. 5). Because NF-κB is involved in critical biologic signaling in controlling immunity, inflammation, and cell survival, aberrant regulation of NF-κB activity is implicated in the pathogenesis of diseases ranging from inflammatory and autoimmune diseases to septic shock, viral infection, tumorigenesis and neurodegenerative disorders (Li and Verma, 2002; Blaschke et al., 2004; Monaco et al., 2004; Aud and Peng, 2006; Mankan et al., 2009).

NF-κB controls many genes involved in immune responses and inflammation, and chronically active NF-κB is found in many inflammatory diseases. Therefore, the regulation of NF-κB is often considered a therapeutic target for inflammatory diseases and, in this regard, numerous phytochemicals that affect NF-κB activity have been identified. Anti-inflammatory effects of isoeleutherin, a phytochemical isolated from the flowering plant *Eleutherine bulbosa*, are mediated by inhibiting NF-κB in LPS-treated macrophages (Song et al., 2009). Capsaicin suppressed obesity-induced inflammation in adipose tissue macrophages, which was associated with inactivation of NF-κB and activation of peroxisome proliferator–activated receptor (PPAR)-γ (Kang et al., 2007). Resveratrol reduced NF-κB activity and obesity-related inflammation markers in adipose tissue of genetically obese rats (Gómez-Zorita et al., 2013). Resveratrol also attenuated LPS- and Aβ-induced microglial inflammation by inhibiting the NF-κB signaling cascade, apparently by interfering with IκB kinase and IκB phosphorylation (Capiralla et al., 2012). Several studies reported that anti-inflammatory effects of curcumin are mediated by suppression of NF-κB activation. In an osteoarthritis model, curcumin suppressed inflammatory cytokines

and NF-κB activation in chondrocytes treated with advanced glycation end products (Yang et al., 2013). Curcumin also reduced expression of cyclooxygenase-2 (COX-2) and MMP-9 in human articular chondrocytes by suppressing NF-κB activation (Shakibaei et al., 2007). Avenanthramides, phenolic compounds present in oats, reduced local inflammation in murine models of contact hypersensitivity by a mechanism involving reduced phosphorylation of the p65 subunit of NF-κB (Sur et al., 2008).

NF-κB is also important in regulating genes that control cell proliferation and survival (Fig. 5). Aberrant NF-κB activation occurs in many different types of human tumors, resulting in elevated expression of genes that promote cell proliferation and survival (Sethi et al., 2008). Accordingly, blocking NF-κB can suppress tumor cell proliferation and trigger apoptosis, particularly when combined with treatment with chemotherapeutic agents or radiation. Curcumin suppresses NF-κB activity in human pancreatic carcinoma cell lines, which renders them vulnerable to apoptosis (Li et al., 2005a). Curcumin was also shown to sensitize breast cancer cells to chemotherapeutic drugs via NF-κB modulation (Royt et al., 2011). Genistein inhibited cell proliferation and induced apoptosis, and soy phytochemicals reduced tumorigenesis, which is associated with induction of tumor cell apoptosis and inhibition of tumor angiogenesis in an orthotopic tumor model. Both in vitro and in vivo anticancer effects of soy phytochemicals are mediated by suppressed NF-κB activity (Singh et al., 2006). The botanical chemical isosilybin A triggered apoptotic death and decreased nuclear translocation of NF-κB in three different human prostate cancer cell lines (Deep et al., 2010). The flavonoid quercetin inhibited cell proliferation and induced mitochondria-mediated apoptosis in human cervical cancer cells through p53 induction and NF-κB inhibition (Vidya Priyadarsini et al., 2010). Because NF-κB promotes cell survival, inhibition of NF-κB can adversely affect normal cells; therefore, NF-κB inhibitors have considerable potential for unwanted side effects of cancer therapies.

Long-term activation of NF-κB in microglia and astrocytes results in the production of proinflammatory cytokines and ROS that can damage neurons. Because NF-κB–mediated glial cell hyperactivation contributes to the pathogenesis of stroke, traumatic brain injury, and neurodegenerative disorders, there has been interest in identifying natural products and developing drugs that inhibit NF-κB. On the other hand, activation of NF-κB in neurons promotes cell survival and can protect neurons in experimental models of acute and chronic neurodegeneration (Camandola and Mattson, 2007). In the remainder of this section, we provide examples of the roles of NF-κB in neuroinflammatory and neurodegenerative conditions, and review evidence that some phytochemicals can modify neurologic disease processes, in part, by modifying NF-κB activity.

Several studies have reported that phytochemicals that inhibit NF-κB in glial cells can protect neurons and brain against neuroinflammation and neurodegeneration (Table 3). Anthocyanin-rich açai (*Euterpe oleracea*) fruit pulp mitigated LPS-induced inflammatory stress and NF-κB activation in mouse brain BV2 microglial cells (Poulose et al., 2012). Ammonia-induced neurotoxicity including oxidative stress and increased cytokine release in astrocytes was inhibited by resveratrol by reducing NF-κB activation (Bobermin et al., 2012). Luteolin blocked LPS-induced NF-κB activation and inflammation responses in BV2 microglia, and improved neuron survival in a model of neuroinflammation (Zhu et al., 2011). Langiferin and morin were found to protect neurons against excitotoxic neuronal death, which was associated with downregulation of NF-κB (Campos-Esparza et al., 2009). Isoquercetin protected cultured cortical neurons from oxygen-glucose deprivation via suppression of the Toll-like receptor 4/NF-κB signaling pathway (Beckman et al., 2013). A neuroprotective effect of silymarin on LPS-induced neurotoxicity was reported in mesencephalic mixed neuron-glia cultures. Silymarin attenuated the LPS-induced microglial activation and the production of inflammatory cytokines through the inhibition of NF-κB activation, and reduced the damage to dopaminergic neurons (Wang et al., 2002). In cultures containing rat cerebral cortical neurons and glial cells, the flavonoid hyperoside protected the neurons against oxygen/glucose deprivation and reduced NF-κB activation (Liu et al., 2012a). Soybean isoflavones alleviated the cytokine cascade and glial inflammatory response induced by Aβ1–42, and improved spatial learning and memory by downregulation of NF-κB activity in rats (Ding et al., 2011). EGCG also ameliorated Aβ1–42–induced memory dysfunction and activation of NF-κB in mice (Lee et al., 2009). EGCG inhibits T-cell proliferation by suppressing cyclin-dependent kinase 4 and upregulating IκB, and oral administration of EGCG protected the brain in an experimental autoimmune encephalomyelitis animal model of multiple sclerosis by reducing T cell–related neuroinflammation (Aktas et al., 2004). In a gerbil model of transient global cerebral ischemia, oral administration of *Crataegus* flavonoids reduced activity of inflammatory glia by a mechanism involving reduction of NF-κB activation (Zhang et al., 2004b). The flavonoid wogonin also suppressed the inflammatory activation of microglia and LPS-induced NF-κB activation, and was neuroprotective in animal models of transient global ischemia and excitotoxic seizures (Lee et al., 2003).

In neurons, NF-κB is activated in response to ongoing excitatory synaptic transmission, and is believed to play important roles in synaptic plasticity, learning, and memory (Kaltschmidt et al., 1994, 2006; Albensi and Mattson, 2000; Meffert et al., 2003; O'Mahony et al.,

TABLE 3
Phytochemicals that modify NF-κB signaling

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
Capsaicin	Adipose tissues macrophages of obese mice	Suppress the inflammatory responses	NF-κB inactivation	Kang et al. (2007)
Resveratrol	Adipose tissue of Zucker (*fa*/*fa*) rats	Body fat reduction and anti-inflammatory activity	Reduced NF-κB and inflammatory responses	Gómez -Zorita et al. (2013)
	Murine RAW 264.7 macrophages and microglial BV-2 cells	Inhibit microglial activation	Suppressed NF-κB signaling	Capiralla et al. (2012)
Curcumin	AGE-treated rabbit chondrocytes	Block inflammation by inhibition of I-κBα phosphorylation	Inhibition of NF-κB activation	Yang et al. (2013)
	Human articular chondrocytes	Reduce inflammatory responses	Suppressed NF-κB activation	Shakibaei et al. (2007)
	T cell	Anti-inflammatory and immunosuppressive function	Suppressed NF-κB activation	Kliem et al. (2012)
	MSC-like progenitor cells	Facilitate chondrogenesis of MSC-like progenitor cells	Suppressed NF-κB activation	Buhrmann et al. (2010)
Silibinin	SKH-1 hairless mice	Protect UVB-induced inflammation and photocarcinogenesis	Decreased phosphorylation of p65 subunit	Gu et al. (2007)
Curcumin	Human pancreatic carcinoma cells	Inhibit pancreatic carcinoma growth and tumor angiogenesis	Decreased NF-κB activity	Li et al. (2005a)
	Breast cancer cells	Downregulate the expression of tumor markers	Decreased NF-κB	Royt et al. (2011)
	Human pancreatic carcinoma cells and murine xenograft models	Suppress pancreatic carcinoma growth and tumor angiogenesis	Downregulation of NF-κB	Li et al. (2004)
Genistein	253J B-V human bladder cancer cells and orthotopic tumor model	Inhibit cell proliferation and induce apoptosis	Downregulation of NF-κB	Singh et al. (2006)
Quercetin	Human cervical cancer (HeLa) cells	Induce G2/M phase cell cycle arrest and mitochondrial apoptosis	NF-κB inhibition	Vidya Priyadarsini et al. (2010)
EGCG	T24 human bladder cancer cells	Suppress invasion and metastasis	Inactivation of NF-κB	Qin et al. (2012)
Mollugin	Human oral squamous cell carcinoma cells	Induce apoptotic cell death	Suppressed activation of NF-κB	Lee et al. (2013)
Resveratrol	Hepatocellular carcinoma	Inhibit tumor growth and angiogenesis	Suppression of the activation of NF-κB	Yu et al. (2010a)
Anthocyanin-rich açai	BV-2 mouse microglial cells	Mitigate LPS-induced oxidative stress and inflammation	Suppression of NF-κB	Poulose et al. (2012)
Resveratrol	C6 astroglial cells and primary cultured cortical astrocyte	Modulate inflammatory stress by ammonia-induced neurotoxicity	Decreased ERK and NF-κB signaling	Bobermin et al. (2012)
Luteolin	BV-2 mouse microglial cells	Inhibit LPS-induced neuroinflammation	Blocked NF-κB activation and inflammatory molecules	Zhu et al. (2011)
Kaempferol	Transient focal stroke rat model	Prevent ischemic brain injury and neuroinflammation	Inhibition of STAT3 and NF-κB activation	Yu et al. (2013)
Naringenin	Rat model of focal cerebral ischemia/reperfusion injury	Elevate the endogenous antioxidant level and inhibit the activation of glial cells	Inhibition of NF-κB activation	Raza et al. (2013)
Mangiferin and morin	Primary cultured cortical neurons	Reduce excitotoxic-induced neuronal cell death	Inhibited the nuclear translocation of NF-κB	Campos-Esparza et al. (2009)
Silymarin	Mesencephalic mixed neuron-glia cultures	Reduce microglial activation and inflammatory mediators by LPS	Inhibition of NF-κB activation	Wang et al. (2002)
Soybean isoflavone	Aβ-injected rat brain	Improve spatial learning and memory	Inhibited TLR4 and NF-κB	Ding et al. (2011)
EGCG	Aβ-injected mice brain	Prevent loss of learning and memory and apoptotic neuronal cell death	Inhibited ERK and NF-κB activation	Lee et al. (2009)
	Autoimmune encephalomyelitis mice model	Reduce neuroinflammation and neuronal cell damage	Intracellular accumulation of IκBα and inhibition of NF-κB activation	Aktas et al. (2004)
Wogonin	BV-2 mouse microglial cells	Inhibit inflammatory activation	Decreased NF-κB activation	Lee et al. (2003)
Caffeic acid	Primary cultured rat cerebellar granule neurons	Decrease apoptotic cell death	Blocked NF-κB and caspase activity	Amodio et al. (2003)

AGE, advanced glycation end product; MSC, mesenchymal stem cell; STAT3, signal transducer and activator of transcription 3; TLR4, Toll-like receptor 4.

2006; Ahn et al., 2008; Boersma et al., 2011). In addition to stimuli that activate NF-κB in peripheral tissues, NF-κB in the nervous system can be stimulated by neurotrophic factors, such as BDNF and nerve growth factor (NGF) as well as the neurotransmitter glutamate (O'Neill and Kaltschmidt, 1997). Activation of *N*-methyl-D-aspartate inotropic glutamate receptors induces BDNF expression by a NF-κB–dependent pathway, implying that NF-κB is required for activity-dependent neuronal survival and long-term memory (Levenson et al., 2004; Marini et al., 2004). Numerous studies have demonstrated that activation of NF-κB in neurons can protect against dysfunction and degeneration in cell culture and animal models of acute and

chronic neurodegenerative conditions, including severe epileptic seizures (Yu et al., 1999), AD (Barger et al., 1995), and HD (Yu et al., 2000). Mice lacking the p65 NF-κB subunit develop a PD-like disease characterized by degeneration of dopaminergic neurons and motor dysfunction as they age, suggesting a critical role for NF-κB in neuronal maintenance during aging (Baiguera et al., 2012). Activation of NF-κB induces the expression of SOD2, which protects mitochondria under conditions of oxidative and metabolic stress (Mattson et al., 1997). Although the available data suggest that NF-κB activation in neurons can enhance synaptic plasticity and is neuroprotective, the identification of phytochemicals that activate NF-κB in neurons is as yet unexplored.

4. Peroxisome Proliferator–Activated Receptors. The PPARs are ligand-activated transcription factors belonging to a nuclear receptor family that regulates target gene expression through binding to peroxisome proliferator response elements (PPREs). Three types of PPARs have been identified (α, β/δ, and γ), which are encoded by different genes. PPARα, the first PPAR identified, was shown to induce peroxisome proliferation (Issemann and Green, 1990). In rodents, PPARα is expressed mainly in tissues with high metabolic activity, including liver, kidney, heart, skeletal muscle, brain, and brown adipose tissue. PPARα is an important fatty acid sensor of metabolic state; PPARα activates fatty acid catabolism and stimulates gluconeogenesis and ketone-body synthesis as adaptive responses to fasting (Berger and Moller, 2002; Michalik et al., 2004). Interestingly, PPARα may also inhibit inflammatory pathways in macrophages and aortic smooth muscle cells by inhibiting NF-κB signaling (Chinetti et al., 1998; Staels et al., 1998). PPARβ/δ is expressed in a wide range of tissues and cells, with high expression levels in brain, adipose tissue, and skin. PPARβ/δ may have roles in embryonic development, lipid metabolism, and cell proliferation, differentiation, and survival (Berger and Moller, 2002; Michalik et al., 2004).

PPARγ has two isoforms (PPARγ1 and PPARγ2) due to alternative RNA splicing. PPARγ2 is expressed mainly in adipose tissue, whereas PPARγ1 is expressed in all tissues (Fajas et al., 1997). PPARγ plays pivotal roles in adipocyte differentiation, fatty acid storage, and glucose metabolism. Mice lacking PPARγ only in fat cells exhibit abnormalities in the formation and function of adipose tissue and fail to generate adipose tissue when fed a high-fat diet (Jones et al., 2005). In addition, PPARγ regulates several genes involved in the insulin signaling pathway and also exerts anti-inflammatory actions (Berger and Moller, 2002). PPARγ dysfunction is implicated in several metabolic and inflammatory diseases, and activation of PPARγ is being pursued as a treatment approach for obesity, diabetes, and atherosclerosis (Berger and Moller, 2002; Giannini et al., 2004; Michalik et al., 2004). Thiazolidinediones, including rosiglitazone and pioglitazone, are PPARγ agonists used to treat type 2 diabetes (Sood et al., 2000; Moller and Greene, 2001).

Several phytochemicals have been shown to activate PPARs (Table 4). Curcumin suppressed oleic acid–induced lipid accumulation and reduced oxidative stress by increasing PPARα in hepatocarcinoma cells (Kang et al., 2013). Curcumin also activated PPARγ and ameliorated hyperglycemia in diabetic KK-Ay mice (Kuroda et al., 2005; Nishiyama et al., 2005). In addition, curcumin activated PPARγ and suppressed hyperglycemia-induced hepatic stellate cell activation to reduce hepatic fibrosis (Shapiro and Bruck, 2005). Diosgenin, extracted from the *Dioscorea* wild yam, reduced oxidative stress and lipid accumulation in a rat type 2 diabetes model, and in silico docking studies revealed a direct interaction of diosgenin with PPARα and PPARγ (Verma et al., 2012). Although the active phytochemical(s) was not established, administration of whole grape powder to rats increased cardiac PPARα and PPARγ DNA-binding activity and decreased NF-κB DNA-binding activity resulting in downregulation of inflammatory cytokines (Seymour et al., 2010). Dehydroabietic acid is a potent activator of both PPARα and PPARγ, and inhibits macrophage activation (Kang et al., 2008a). Modified derivatives of the phytochemicals betulinic acid and glycyrrhetinic acid were shown to have PPARγ agonist activity (Chintharlapalli et al., 2007a,b). Moreover, it was recently reported that a novel synthetic phenolic compound MHY 966 [2-bromo-4-(5-chloro-benzo[*d*]thiazol-2-yl) phenol] can act as a PPARα/PPARγ dual agonist and suppresses UV radiation–induced inflammatory responses and lipid peroxidation (Park et al., 2013).

PPARγ activation can suppress neuroinflammation, and may confer neuroprotective effects in stroke and neurodegenerative diseases such as AD and PD. Neuroprotective effects of the PPARγ agonists rosiglitazone, pioglitazone, and 15-deoxy-prostaglandin J_2 were reported in studies of animal models of ischemic stroke (Bordet et al., 2006; Culman et al., 2007). It was shown that long-term treatment with pioglitazone improved cognitive deficits and AD-related pathology in a mouse model of AD (Sato et al., 2011; Gupta and Gupta, 2012; Searcy et al., 2012; Xiang et al., 2012). Neuroprotective effects of PPAR agonists have also been demonstrated in experimental models of PD (Chaturvedi and Beal, 2008; Ridder and Schwaninger, 2012). The PPAR-γ agonist pioglitazone was shown to be protective in MPTP-induced PD monkey and mouse models (Breidert et al., 2002; Dehmer et al., 2004; Quinn et al., 2008; Swanson et al., 2011). Resveratrol activated both PPARα and PPARγ in primary cortical neurons and vascular endothelial cells, and protected the brain against ischemic stroke; neuroprotection by resveratrol and the PPARα agonist fenofibrate was abolished in PPARα knockout mice (Inoue et al., 2003). Resveratrol was

TABLE 4
Phytochemicals that activate PPAR signaling

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
Curcumin	Human hepatoma HepG2 cells	Inhibit oleic acid–induced hepatic lipogenesis and hepatic antioxidative ability	Increased the expression of PPARα	Kang et al. (2013)
	Type 2 diabetic KK-A^y mice	Exhibit hypoglycemic effects and stimulated human adipocyte differentiation	Activated PPARγ	Nishiyama et al. (2005); Kuroda et al. (2005)
	HSCs		Activated PPARγ	Shapiro and Bruck (2005)
	Eker rat–derived uterine leiomyoma cell lines	Inhibit of cell proliferation	Acted as PPARγ ligand	Tsuiji et al. (2011)
Diosgenin	STZ-induced type 2 diabetes model of rats	Modulate glucose level and decreased oxidative stress and lipid accumulation	Interacted PPARα and PPARγ	Sangeetha et al. (2013)
Whole grape powder	Dahl salt-sensitive hypertensive rats	Reduce blood pressure, cardiac hypertrophy, and diastolic dysfunction	Enhanced cardiac PPARα and PPARγ, but decreased NF-κB	Seymour et al. (2010)
Betulinic acid and glycyrrhetinic acid	Human colon and pancreatic cancer cells	Induce cytotoxicity	Activated PPARγ	Chintharlapalli et al. (2007a,b)
MHY 966	Melanin-possessing hairless mice 2	Modulate UVB-induced inflammatory responses	Activated PPAR α and PPARγ	Park et al. (2013)
Resveratrol	MCAO stroke mice model	Reduce brain infarct volume	Activated PPARα and PPARγ	Inoue et al. (2003)
	Primary cultured cortical neurons	Inhibit MMP-9 and protected neurons from OGD injury	Upregulation of PPARα	Cheng et al. (2009)
Genistein	Primary cultured cortical astrocytes	Decrease inflammatory responses to Aβ	Increased PPARγ expression	Valles et al. (2010)
Daidzein	OGD from rat cortical neurons	Decrease cell death and improve synaptic function	Increased PPARγ activity in the nucleus	Hurtado et al. (2012)
Naringenin	Human hepatocyte carcinoma Huh7 cell line	Increase fatty acid oxidation and decrease cholesterol and bile acid production	Activated PPARα and PPARγ	Goldwasser et al. (2010)
Curcumin	Rat middle cerebral artery occlusion model	Decrease the infarct volume, neuronal damage and improve neurologic deficits	Upregulated PPARγ expression and PPARγ activity	Liu et al. (2013c)
	Primary cultured astrocytes	Decrease Aβ-induced inflammatory mediators	Activated PPARγ	Wang et al. (2010a)
	Mice intracerebroventricular STZ-induced dementia model	Improve STZ-induced memory deficits and modulate AChE activity and oxidative stress	Activated PPARγ	Rinwa et al. (2010)
	HSCs	Inhibit ERK activity and stimulate the *trans*-activity of PPARγ	Activated PPARγ	Lin et al. (2012a)
	HSCs	Eliminate effects of AGEs	Activated PPARγ	Lin et al. (2012b)
		Inhibit α1(I)-collagen gene expression and CTGF	Activated PPARγ and interrupted TGF-β	Zheng and Chen (2006)
	HSCs	Increase TNF-α expression	Activated PPARγ	Siddiqui et al. (2006)
	RAW 264 (macrophages) and septic animals	Attenuate oxidative stress, suppressed of Ob-R gene expression	Activated PPAR and interrupted of leptin signaling	Tang et al. (2009)
	HSCs	Evaluate ox-LDL and suppress Lox-1 expression	Activated PPARγ and interrupting Wnt signaling	Kang and Chen (2009)
	HSCs	Suppress glut2 expression and attenuate oxidative stress	Activated PPARγ	Lin and Chen (2011)
Hesperetin (from a citrus)	THP-1 (macrophages)	Increase ABCA1 expression and activate LXRα	Activated PPARγ	Iio et al. (2012)
ABA	3T3-L1 (adipocytes) and *db*/*db* mice	Decrease fasting blood glucose concentration and ameliorate glucose tolerance	Activated PPARγ	Guri et al. (2007)
PGF	THP-1 (differentiated macrophage cells) and Zucker diabetic fatty rats and Zucker lean rats	Decrease GLUT-4 and improve the insulin receptors	Activated PPARγ	Huang et al. (2005)
Grapes	Grape-fed rat	Decrease cardiac TNF-α, TGF-β protein expression, and cardiac fibrosis and increase IκBα expression	Activated PPARγ and NF-κB	Seymour et al. (2010)

ABA, abscisic acid; ABCA1, ATP binding cassette 1; AChE, acetylcholinesterase; AGE, advanced glycation end product; CTGF, connective tissue growth factor; GLUT, glucose transporter; HSC, hepatic stellate cells; LDL, low-density lipoprotein; LXR, liver X receptor; MCAO, middle cerebral artery occlusion; Ob-R, leptin receptor; OGD, oxygen–glucose deprivation; PGF, Punica granatum flower; STZ, streptozotocin; TGF, transforming growth factor; THP-1, a human monocyte cell line; TNF, tumor necrosis factor.

also shown to inhibit MMP-9 expression by upregulating PPARα expression in cortical neurons subjected to oxygen and glucose deprivation (Cheng et al., 2009). The soy isoflavone genistein was effective in preventing Aβ-associated inflammation, which was associated with increased PPARγ expression, in primary cultured astrocytes (Valles et al., 2010). Interestingly, the phytoestrogen daidzein protected cortical neurons in an experimental in vitro stroke model; this neuroprotection was due to an increased PPARγ activity without direct binding to the receptor (Hurtado et al., 2012). The flavanone naringenin activates both PPARα and PPARγ, and induces PPRE-driven gene expression in human hepatocytes (Goldwasser et al., 2010). A recent study reported that naringenin can protect the brain and prevent oxidative stress and NF-κB–mediated inflammation in a rat model of focal ischemic stroke (Raza et al., 2013). Curcumin, known as a potent PPARγ agonist, protected neurons and suppressed neuroinflammatory responses in a rat stroke model (Liu et al., 2013c). Curcumin reduced Aβ-induced inflammatory responses in primary cultured astrocytes and attenuated memory deficits in a mouse dementia model (Rinwa et al., 2010; Wang et al., 2010a). The latter two studies showed that PPARγ antagonists significantly abolished the beneficial effects of curcumin.

Abnormal inflammatory and cytotoxic processes are often involved in neuropsychiatric diseases such as depression and schizophrenia; thus, considering the pleiotropic effects of PPARγ, its pharmacological activation might be a new therapeutic target in psychiatric disorders (García-Bueno et al., 2010). Several phytochemicals known to activate PPARγ were reported to ameliorate depression-like behaviors in mouse models. For example, curcumin treatment significantly reduced the duration of immobility in both the forced swim test and tail suspension test (Xu et al., 2005). Curcumin treatment also reversed depressive behaviors in a mouse model of neuropathic pain–induced depression by a mechanism requiring serotonergic signaling (Zhao et al., 2013b). However, a role for PPARγ was not established in either of the latter studies. The PPAR agonist rosiglitazone was recently reported to reverse depression-like behavior (forced swim test), but not psychosis-like behavior (prepulse inhibition test), in diabetic mice (Sharma et al., 2012). Although the mechanisms by which PPAR agonists improve mood remain to be established, possibilities include enhancement of hippocampal synaptic plasticity and neurogenesis (Kobilo et al., 2011). Further studies of the modulation of PPAR activity by phytochemicals should be pursued with the goal of developing novel therapeutic interventions for neurodegenerative and neuropsychiatric disorders.

B. Trophic Signaling Pathways

Studies in the field of developmental neurobiology have identified signaling pathways that regulate the outgrowth of axons and dendrites, synapse formation and maintenance, and cell survival. In many instances, these pathways involve neurotrophic factors, which are proteins released by neurons and/or glial cells, often in response to neuronal activity or tissue injury. Neurotrophic factors can activate one or more downstream signaling pathways involving kinases such as Akt, Ca^{2+}-calmodulin–dependent kinases, and mitogen-activated protein kinases (MAPKs). Conversely, there are phosphatases and some kinases that antagonize trophic signaling pathways; examples include phosphatase and tensin homolog, glycogen synthase kinase (GSK)-3β, and c-Jun N-terminal kinase (JNK). Several hormones also exert neurotrophic actions, with insulin being a prominent example. In this section, we describe examples of phytochemicals that have been shown to activate trophic signaling pathways in neurons and therefore have potential for use in neuroregenerative medicine.

1. Neurotrophic Factors. Major neurotrophic factors include the neurotrophins (BDNF, NGF, and neurotrophin 3), fibroblast growth factor 2, insulin-like growth factors (IGF-1 and IGF-2), and glial cell line–derived neurotrophic factor (GDNF). The biologic activities and mechanisms of action of these neurotrophic factors were previously reviewed (Krieglstein, 2004; Spedding and Gressens, 2008; Fernandez and Torres-Alemán, 2012; Terwisscha van Scheltinga et al., 2013; Marosi and Mattson, 2014). The receptors for a neurotrophic factor are widely expressed in many or all types of neurons in some cases, (e.g., the BDNF receptor TrkB, and the fibroblast growth factor 2 and IGF-1 receptors), whereas the receptors have a more limited distribution in other cases (GDNF and neurotrophin 3 receptors). A prominent function of these neurotrophic factors is that they mediate adaptive responses of neurons to stress. Abundant preclinical evidence supporting the potential for neurotrophic factor–based therapeutic interventions in disorders ranging from stroke and traumatic brain injury to AD and PD. As described in this section, some phytochemicals have been shown to induce the expression of one or more neurotrophic factors, or to activate neurotrophic factor receptors, which may represent adaptive stress responses to the phytochemicals.

Endogenous and environmental stimuli that cause cellular stress can stimulate production and release of BDNF, as well as activation of TrkB (Fig. 6). Activation of excitatory glutamatergic synapses results in Ca^{2+} influx and activation of the transcription factors CREB and NF-κB, each of which induces BDNF production (Tao et al., 1998; Marini et al., 2004). There are several studies reporting that beneficial effects of dietary phytochemicals are mediated by BDNF. Grape powder treatment prevented anxiety, memory impairment, and hypertension induced by oxidative stress in rats by a mechanism involving CREB activation and BDNF

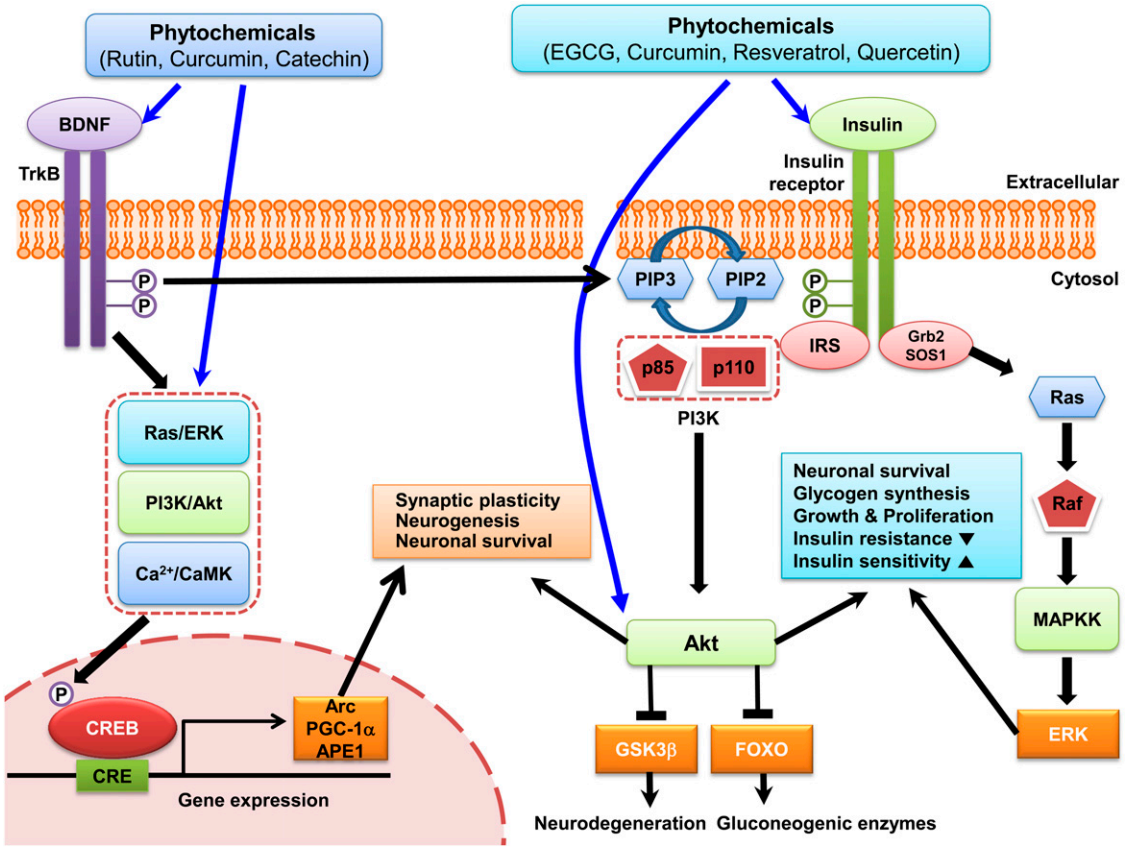

Fig. 6. BDNF and insulin signaling pathways activated by phytochemicals. Several phytochemicals, including those indicated, have been shown to activate the BDNF and/or insulin signaling pathways. Receptors for BDNF and insulin are similar in structure and couple to similar downstream signaling pathways. The BDNF receptor TrkB and the insulin receptor have a tyrosine kinase domain in their cytoplasmic region. Binding of ligand results in receptor dimerization and *trans*-autophosphorylation (p) of the receptors that then recruits adaptor proteins and activates several downstream proteins kinases as indicated. A prominent transcription factor activated by BDNF is CREB, which induces the expression of genes encoding proteins involved in synaptic plasticity (e.g., Arc), cellular energy metabolism (e.g., PGC-1α, which induces mitochondrial biogenesis), and stress resistance (e.g., the DNA repair enzyme APE1). Activation of both TrkB and the insulin receptor can also activate the PI3K (p85–p110) Akt kinase signaling resulting in the inhibition of GSK-3β and FOXO, thereby protecting neurons against degeneration. Activation of the Grb/SOS, Ras, Raf, MEK, and ERK pathways can enhance cellular stress resistance and increase insulin sensitivity. Akt, Akt kinase; APE1, apurinic/apyrimidinic endonuclease 1; CaMK, calcium/calmodulin-dependent kinase; Grb2, growth factor receptor bound protein 2; MAPKK, mitogen-activated protein kinase kinase; PGC-1α, PPARγ coactivator 1α; PIP2, phosphatidylinositol bisphosphate; PIP3, phosphatidylinositol trisphosphate; SOS, son of sevenless homolog 1.

production (Allam et al., 2013). By activating a BDNF survival pathway, cocoa polyphenol extract was neuroprotective against Aβ-induced toxicity (Cimini et al., 2013). Olive polyphenols increased the levels of BDNF and NGF in the limbic system and olfactory bulb (De Nicoló et al., 2013). Long-term administration of green tea polyphenols reduced age-related oxidative stress in the hippocampus of rats, which was associated with increased BDNF expression (Assunção et al., 2010). A blueberry-supplemented diet for 21 weeks improved age-related memory impairment of spatial working memory by a mechanism involving activation of hippocampal CREB and upregulation of BDNF production (Williams et al., 2008).

Neurotrophic signaling cascades can be triggered by specific phytochemicals (Table 5). Rutin (3,3,4,5,7-pentahydroxyflavone-3-rhamnoglucoside), a flavonol found in buckwheat, passion flower, apple, and tea, significantly increased levels of extracellular signal-regulated kinase (ERK)-1, CREB, and BDNF gene expression in the hippocampus of rats (Moghbelinejad et al., 2014). Chronic stress-induced depression decreases BDNF and phosphorylated CREB levels in the hippocampus and frontal cortex in rats, and curcumin treatment prevents the suppression of BDNF levels (Xu et al., 2006b). Curcumin was also effective in preventing Aβ-induced cognitive impairment, neuroinflammation, and impaired BDNF signaling (Hoppe et al., 2013). Interestingly, it was recently shown that curcumin can protect mice against cognitive impairment resulting from neuroinflammation by a mechanism involving BDNF upregulation and requiring tumor necrosis factor-α signaling (Kawamoto et al., 2013). By utilizing specific inhibitors in cultured cortical neurons, it was shown that BDNF, TrkB, MAPK, phosphoinositol 3 kinase (PI3K), and CREB mediate neuroprotective actions of curcumin (Wang et al., 2010c). However, it was reported that curcumin is a specific inhibitor of the CBP/p300 acetyltransferase (Balasubramanyam et al., 2004), and a recent

TABLE 5
Phytochemicals that modify neurotrophic factor signaling

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
Rutin	Frontal cortex of rat brain	Neuroprotective effects against neurotoxicity of Aβ	Increased BDNF, pCREB	Moghbelinejad et al. (2014)
Curcumin	Hippocampus and frontal cortex	Effects on the neurotrophin factor expression	Increased BDNF, pCREB	Xu et al. (2006b)
	β-amyloid–induced rats	Prevent behavioral impairments, neuroinflammation, and τ hyperphosphorylation	Increased BDNF and Akt/GSK-3β	Hoppe et al. (2013)
	TNFR1 and TNFR2 double knockout mice	Protect cultured neurons against glutamate-induced excitotoxicity by TNFR2 activation	Increased BDNF	Kawamoto et al. (2013)
		Increase levels of phosphor-ERK and Akt	Increased BDNF, pCREB	Wang et al. (2010c)
Resveratrol	Prefrontal cortex and hippocampus	Effective in promoting astroglia-derived neurotrophic factor release	Increased BDNF, GDNF	Zhang et al. (2012a)
	Hippocampus of prenatally stressed rat	Improve the expression of DCX-positive neuron	Increased BDNF	Madhyastha et al. (2013)
	Hippocampus neural progenitor cells	Deficits in hippocampus-dependent spatial learning and memory	Decreased BDNF-pCREB signaling	Park et al. (2012a)
Ferulic acid	Hippocampus (CORT-treated mice and stress-induced depression-like behavior of mice)	Effects on the mood disorders such as depression	Increased BDNF mRNA	Yabe et al. (2010)
Lancemaside A	Hippocampus	Ameliorate memory and learning deficits	Increased BDNF, pCREB	Jung et al. (2012)
Heptamethoxyflavone	Hippocampus after ischemia	Induce BDNF production in astrocytes and enhance neurogenesis after brain ischemia	Increased BDNF, pCREB	Okuyama et al. (2012)
Oroxylin A	Primary cortical neuronal culture cell	Responsible for the neuroprotective or memory-enhancing effects	Increased BDNF expression	Jeon et al. (2011)
	Hippocampus	Attenuate the memory impairment and show neuroprotective effects	Increased BDNF, pCREB	Kim et al. (2006)
Procyanidins	Hippocampus and cerebral cortex	Enhance CREB-dependent transcription through the activation of ERK signaling pathway	Increased pCREB	Xu et al. (2010a)
Bilobalide and quercetin	Mice model of AD (hippocampus)	Increase cell proliferation in the hippocampal neurons/enhance neurogenesis and synaptogenesis	Increased pCREB	Tchantchou et al. (2009)
Catechin	Senescence-accelerated mouse prone-8 (hippocampus)	Prevent spatial learning and memory decline of SAMP8 mice by decreasing Aβ (1-42) oligomers and upregulating synaptic plasticity-related proteins	Increased BDNF, pCREB	Li et al. (2009)
Olive polyphenols	Hippocampus, olfactory, striatum, and frontal cortex	NGF and BDNF elevation in the hippocampus and olfactory bulbs and a decrease in the frontal cortex and striatum	Increased BDNF, NGF	De Nicoló et al. (2013)
C-dideoxyhexosyl flavones	PC12 cells	Neurite outgrowth enhancing activities	Increased NGF	Xu et al. (2013)
Baicalein	C17.2 cells hippocampus	Protect NPCs against irradiation-induced necrotic cell death and the spatial learning and memory retention deficits after whole-brain irradiation	Increased BDNF-pCREB signaling	Oh et al. (2013)
Diallyl disulfide	Hippocampus NPC	Decreased the proliferation of NPCs in the dentate gyrus adverse effects on hippocampal neurogenesis and neurocognitive functions	Decreased BDNF-pCREB signaling	Ji et al. (2013)

CORT, corticosterone; DCX, doublecortin; NPC, neural progenitor cell; pCREB, phosphorylated CREB; TNFR, tumor necrosis factor receptor.

study proposed that CBP/p300 activation by a small molecule synthesized from salicylic acid increases maturation and differentiation of adult neuronal progenitors and long-term memory by inducing BDNF expression (Chatterjee et al., 2013). Moreover, curcumin administration blocked the upregulation of BDNF transcription and analgesic tolerance in a model of chronic morphine administration (Matsushita and Ueda, 2009). Therefore, effects of curcumin on BDNF signaling may be context dependent.

Resveratrol can increase GDNF and BDNF expression in astrocytes through the activation of ERK1/ERK2 and CREB (Zhang et al., 2012a). Resveratrol-induced BDNF expression and its beneficial effects were reported in studies of animal models of depression (Moriya et al., 2011; Hoppe et al., 2013; Madhyastha

et al., 2013). On the other hand, resveratrol can down-regulate CREB activity and BDNF production in the hippocampus of unstressed mice (Park et al., 2012a). This suggests that resveratrol might differentially regulate BDNF expression depending upon the level of stress encountered by neurons. Finally, in addition to stimulating production of neurotrophic factors by inducing adaptive stress response signaling pathways, some phytochemicals may directly activate neurotrophic factor receptors. For example, recent findings suggest that 7,8-dihydroxyflavone is a TrkB agonist and can mimic neuroprotective actions of BDNF (Jang et al., 2010b; Liu et al., 2012b). Further research will likely identify more phytochemicals that stimulate neurotrophic factor signaling, and will pursue their development as therapeutic interventions for conditions that may benefit from enhanced neurotrophic signaling.

2. Sirtuins. Silent information regulator 2, the first member of a family of NAD^+-dependent protein deacetylases termed *sirtuins*, was identified in *S. cerevisiae* and was originally described as a regulator of transcriptional silencing of mating-type loci in the yeast (Haigis and Sinclair, 2010; Guarente, 2011). In mammals, there are seven sirtuins (SIRT1–SIRT7) that have different enzymatic activities and can be divided into four classes (class I, SIRT1–SIRT3; class II, SIRT4; class III, SIRT5; and class IV, SIRT6 and SIRT7) (Frye, 2000). SIRT1–SIRT6 possess NAD^+-dependent deacetylase activity. SIRT4 and SIRT6 are also known for ADP-ribosyl transferase activity, and SIRT5 displays an NAD^+-dependent protein lysine desuccinylase and demalonylase activity (Imai and Guarente, 2010; Du et al., 2011; Guarente, 2011; Peng et al., 2011). Sirtuins have discrete subcellular localizations that contribute to their diverse functions (Donmez, 2012; Hall et al., 2013). SIRT1, SIRT6, and SIRT7 reside predominantly in the nucleus and regulate transcription through modification of transcription factors, histones, and cofactors (Chalkiadaki and Guarente, 2012). SIRT3–SIRT5 are primarily found in mitochondria, and have a role in regulation of oxidative stress and the activities of metabolic enzymes (Verdin et al., 2010; Bell and Guarente, 2011). SIRT2 is located primarily in the cytoplasm and has functions in cell cycle regulation, oligodendrocyte differentiation, and programmed cell death (Dryden et al., 2003; Li et al., 2007b; Narayan et al., 2012).

Sirtuins are NAD^+-dependent protein deacetylases that remove acetyl groups from lysine residues by an enzymatic mechanism that splits NAD^+ and releases nicotinamide, *O*-acetyl-ADP-ribose, and the deacetylated substrate (Imai et al., 2000). NAD^+ is an important cofactor responsible for maintaining redox balance with NADH, and is a rate-limiting substrate for sirtuins. The intracellular concentration of NAD^+ oscillates in response to the nutritional availability of the cell (Houtkooper et al., 2010). When NAD^+ levels are increased, such as during calorie restriction or fasting, the enzymatic activity of sirtuins is increased. SIRT1 activation results in a coordinated reprogramming of cellular energy metabolism through deacetylation of many transcription factors and cofactors including PPARγ coactivator 1α, forkhead box subgroup O (FOXO), and nuclear receptors (Brunet et al., 2004; Motta et al., 2004; Rodgers et al., 2005; Li et al., 2007c) (Fig. 7). Deacetylation of the latter transcription factors induces the expression of genes that stimulate mitochondrial biogenesis and fatty acid oxidation (Purushotham et al., 2009). SIRT1 also regulates other key pathways that are likely to be involved in cellular stress resistance, including HIF-1α, Hsp1, and DNA repair proteins such as Ku70 and Werner (Donmez et al., 2010; Baur et al., 2012).

Sirtuins, particularly SIRT1, have been extensively studied for their roles in calorie restriction–induced life span extension, as well as the prevention of aging-associated pathologies including metabolic dysfunction (type 2 diabetes and obesity), cardiovascular disease, cancer, and neurodegeneration. There has been a recent flurry of evidence suggesting that activation of SIRT1 and other sirtuins can protect neurons in experimental models of neurodegenerative disorders (for a review, see Duan, 2013). For example, in models relevant to AD, deacetylation of retinoic acid receptor-β by SIRT1 activates transcription of the ADAM metallopeptidase domain 10 gene, which encodes α-secretase, resulting in nonamyloidogenic processing of the APP (Donmez et al., 2010). SIRT1 was also shown to deacetylate and destabilize τ protein, thereby reducing its aggregation, which suggests that SIRT1 can prevent the formation of neurofibrillary tangles (Min et al., 2010). In models of HD, SIRT1 counteracts the adverse effects of mutant huntingtin on BDNF expression and dopamine production (Jiang et al., 2012).

The search for phytochemicals and synthetic drugs that specifically activate sirtuins is underway in laboratories throughout the world (Table 6). Resveratrol has received widespread attention because it can increase SIRT1 activity in various cell types, and has been suggested to be the phytochemical that mediates health benefits of red wine, grapes, and berries (Houtkooper et al., 2012; Villalba and Alcaín, 2012). Findings suggest that resveratrol can prevent the deleterious effects of a high-fat diet on metabolism and increases survival of obese mice (Baur et al., 2006; Lagouge et al., 2006). Resveratrol elicits gene expression profiles that strongly resemble those induced by calorie restriction (Pearson et al., 2008). Synthetic analogs of resveratrol have been developed as novel sirtuin activators, and some of these compounds have been reported to be neuroprotective and promote synaptic plasticity in animal models (Gräff et al., 2013). The activation of SIRT1 by resveratrol and other phytochemicals may not be the result of a direct molecular interaction of the phytochemical with SIRT1. Instead,

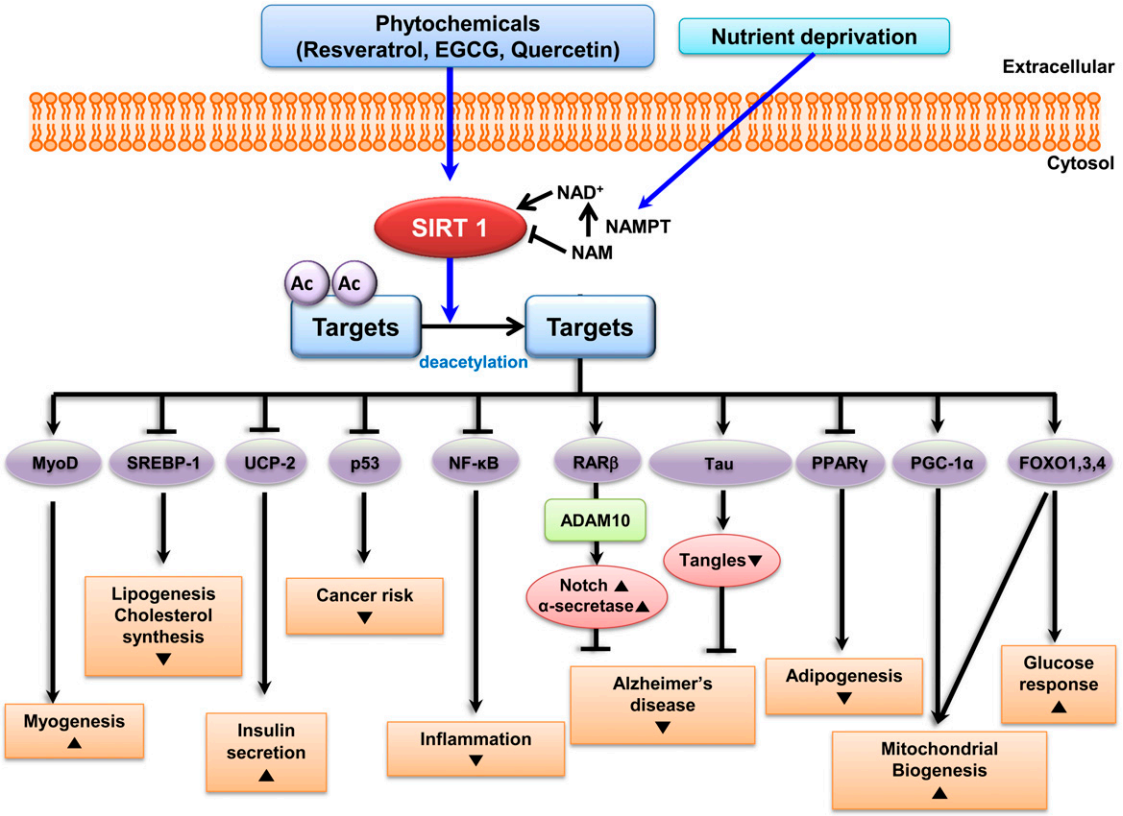

Fig. 7. Activation of SIRT1 modifies multiple downstream target proteins involved in adaptive cellular stress responses. Exposure of cells to several different phytochemicals (resveratrol, EGCG, quercetin, and others) results in the activation of the NAD^+-dependent histone deacetylase SIRT1. Numerous SIRT1 protein targets have been identified, and many of them are likely involved in adaptive stress responses. Some of the target proteins are activated by SIRT1 (MyoD, RARβ, τ, PGC-1α, and FOXO), whereas other deacetylation by SIRT1 inhibits the function of other proteins (SREBP-1, UCP-2, p53, NF-κB, and PPARγ). Consequences of activation or inhibition of the SIRT1 target proteins are shown; for example, activation of MyoD stimulates myogenesis, inhibition of SREBP-1 reduces lipogenesis and cholesterol synthesis, and so forth. Ac, acetyl group; ADAM10, ADAM metallopeptidase domain 10; MyoD, a protein that regulates muscle cell differentiation; NAM, nicotinamide; NAMPT, nicotinamide phosphoribosyltransferase; PGC-1α, PPARγ coactivator 1α; RARβ, retinoic acid receptor β; SREBP-1, serum response element-binding protein 1; UCP-2, uncoupling protein 2.

SIRT1 activation may occur in response to stress induced by the phytochemicals. Pretreatment was required in many reported studies in which resveratrol was demonstrated to be neuroprotective, which is consistent with a preconditioning/hermetic mechanism of action (Kim et al., 2007; Della-Morte et al., 2009; Khan et al., 2012). In addition to resveratrol, several other phytochemicals have been reported to activate SIRT1, including butein and fisetin (Howitz et al., 2003; Bauer et al., 2004; Wood et al., 2004), and are neuroprotective in one or more models (Burdo et al., 2008; Cho et al., 2012). Although activation of SIRT1 by phytochemicals can be neuroprotective, because SIRT1 activity consumes NAD^+, it may hasten the demise of neurons under conditions of limited energy availability as may occur during cerebral ischemia (Liu et al., 2009).

3. Mitogen-Activated Protein Kinase Activation. MAPKs are serine/threonine kinases that mediate cellular responses to a wide variety of stimuli, including growth factors, cytokines, and environmental stressors (osmotic, heat shock, radiation, and metabolic stress). MAPK cascades are divided into those that signal through ERKs, JNKs, or p38 MAPKs (Cossa et al., 2013; Klein et al., 2013). ERK1 and ERK2 are responsive to growth factors, cytokines, viral infection, transforming agents, and carcinogens that activate the Ras/Raf/MEK/ERK pathway to regulate cell proliferation, survival, differentiation, motility, and metabolism (Kolch, 2005). Deregulation of the ERK pathway is common in cancers, and anticancer properties of some phytochemicals are mediated by inhibition of this pathway. For example, EGCG inhibits cell proliferation and epidermal growth factor-dependent activation of ERK1/ERK2 in immortalized cervical cells (ECE16-1) (Sah et al., 2004). The green tea catechins (EGCG and epicatechin gallate) inhibit hepatocyte growth factor-induced Met phosphorylation and downstream activation of Akt and ERK to suppress invasive cancer growth in breast carcinoma and prostate cancer cells (Bigelow and Cardelli, 2006; Duhon et al., 2010). Green tea polyphenols and caffeine inhibited cell proliferation, enhanced apoptosis, and lowered levels of c-Jun and phosphorylated ERK1/ERK2 in a lung tumor progression model of mice (Lu et al., 2006). The isoflavone metabolite 6-methoxyequol exhibits anti-angiogenic activity by targeting the phosphorylation of MEK1/MEK2 and its downstream substrate ERK1/ERK2 (Bellou et al., 2012). A final example is

TABLE 6
Phytochemicals that modify SIRT signaling

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
Resveratrol (from a red wine)	Human health stem cells	Abolish protein deacetylation and autophagy	Inhibited SIRT 1	Pietrocola et al. (2012)
	SH-HY5Y cells and PC12 cells	Protect against rotenone-induced apoptosis, enhanced degradation of α-synucleins, and decreased of protein level of LC3-II	Inhibited SIRT 1 and AMPK	Wu et al. (2011)
	Dopaminergic neurons	Prevent accumulation of ROS and depletion of cellular glutathione	Activated SIRT 1	Okawara et al. (2007)
	Mild ischemic stroke–induced rat	Decrease blood–brain barrier disruption and edema and increase viability	Inhibited SIRT 1	Clark et al. (2012)
	3T3-L1 adipocytes	Reduces triacylglycerol content, C/EBPβ and increase ATGL, CPT-1, and PGC1-α expression	Activated SIRT 1	Lasa et al. (2012)
	Soleus muscle	Maintain soleus mitochondrial capacity, born mineral density, and strength of the femur	Preserved SIRT 1	Momken et al. (2011)
		Decrease MCP-1, ICAM-1 in the retina, retinal 8-OHdG generation, nuclear NK-κB p65	Activated SIRT 1	Kubota et al. (2009)
		Increase cysteine and decrease glutathione, β-amyloid plaque formation, and oxidative stress	Activated SIRT 1	Karuppagounder et al. (2009)
GSPE	HUVECs BAT	Increase eNOS expression and NO production	Activated SIRT 1 and AMPK Inhibited SIRT 1	Cui et al. (2012)
EGCG	PC12 cells	Increase cell viability, PGC-1α, SOD1, and GPX1 expression and decrease ROS production	Activated SIRT 1	Ye et al. (2012)
Red wine polyphenols	HUVECs	Increase p21 protein, eNOS, and COX-2 expression	Inhibited SIRT 1	Botden et al. (2012)
Silibinin	Pancreatic β cells and STZ-induced diabetic mice	Decrease glycosylated hemoglobin A1C, serum triglyceride, cholesterol, blood glucose, autophagy, and apoptosis ratio	Activated SIRT 1	Wang et al. (2012c)
	Rat neonatal cardiac myocytes	Decrease LDH release and MDA production and increase SOD and Bcl-2 expression	Activated SIRT 1	Zhou et al. (2007)
	Myocardial cells	Increase SOD, mitochondrial membrane potential, and Bcl-2 expression, and decrease Bax expression	Activated SIRT 1	Zhou et al. (2006)
Baicalin	SH-SY5Y cells	Increase cell viability and reduce the contents of LDH, NO, and Caspase-3	Activated SIRT 1	Chen et al. (2011a)
Naringenin (from grapefruit)	L6 myotubes and skeletal muscle cells	Increase glucose uptake	Activated SIRT 1 and AMPK	Zygmunt et al. (2010)
Icariin	Neurons	Scavenging effect on free radicals and activate cellular antioxidant enzymes including catalase	Activated SIRT 1	Zhang et al. (2010a)
	Neurons and middle cerebral artery occlusion in mice	Increase PGC1-α	Activated SIRT 1	Zhu et al. (2010)
	Neurons	Increase neuronal viability and suppress neuronal death after oxygen and glucose deprivation	Activated SIRT 1 and MAPK/p38 pathway	Wang et al. (2009)
Quercetin	Quercetin-fed mice	Increase mRNA expression of PGC-1α, mtDNA, and cytochrome *c*	Activated SIRT 1	Davis et al. (2009)
	Elastase/LPS-exposed mice	Decrease levels of thiobarbituric acid, lung inflammation, goblet cell metaplasia, mRNA expression of proinflammatory cytokines and muc5AC and activity of MMP-9 and MMP-12	Activated SIRT 1	Ganesan et al. (2010)

(*continued*)

TABLE 6—*Continued*

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
Genistein	Prostate cancer cells	Activate TSGs and attenuated phosphorylated-Akt and NF-κB	Inhibited SIRT 1	Kikuno et al. (2008)
Silymarin (from a milk thistle)	A375-S3 cells (UV-irradiated human malignant melanoma)	Decrease Bax expression and cytochrome *c* and increase ICAD and PARP	Activated SIRT 1	Li et al. (2007a)

AMPK, AMP-activated protein kinase; ATGL, adipose triacylglycerol lipase; BAT, brown adipose tissue; CPT, carnitine palmitoyltransferase; C/EBP, CCAAT-enhancer-binding protein; eNOS, endothelial nitric-oxide synthase; GPX, glutathione peroxidase; GSPE, grape seed proanthocyanidin extract; HUVEC, human umbilical vein endothelial cell; ICAD, inhibitor of caspase activated DNAse; ICAM, intercellular adhesion molecule; LC3-II, microtubule-associated protein 1 light chain 3-II; LDH, lactate dehydrogenase; MCP, monocyte chemotactic protein; MDA, malondialdehyde; mtDNA, mitochondrial DNA; PARP, poly(ADP-ribose) polymerase; PGC-1α, PPARγ coactivator 1α; STZ, streptozotocin; TSG, tumor suppressor gene.

that Epstein–Barr virus–associated B cell malignancies are attenuated by resveratrol in association with induction of p38 MAPK phosphorylation and suppression of the ERK1/ERK2 signaling pathway (De Leo et al., 2011).

ERK1/ERK2 activation promotes cell survival and synaptic plasticity in neurons (Grewal et al., 1999), and an increasing number of phytochemicals are being identified that activate ERKs in neural cells (Table 7). Neuroprotective effects of the citrus flavanone hesperetin are mediated by ERK1/ERK2 activation (Rainey-Smith et al., 2008). Hesperetin can prevent neuronal apoptosis by a mechanism involving the activation of both Akt and ERK1/ERK2 in cortical neurons (Vauzour et al., 2007). L-Theanine attenuated both rotenone- and dieldrin-induced DNA fragmentation and apoptosis in human neuroblastoma cells by preventing downregulation of ERK1/ERK2 phosphorylation (Cho et al., 2008). The phenolic phytochemical gastrodin can protect primary cultured rat hippocampal neurons against Aβ-induced neurotoxicity via the ERK1/ERK2/Nrf2 pathway (Zhao et al., 2012). In addition, several studies suggested that neurotrophic and neurogenic actions of phytochemicals are mediated by ERK1/ERK2. Resveratrol increased BDNF and GDNF production while increasing the phosphorylation of ERK1/ERK2 and CREB in astrocytes (Zhang et al., 2012a). Moreover, the antidepressant-like effect of resveratrol was suggested to be mediated through increased ERK phosphorylation and BDNF expression (Davis et al., 2013). Oroxylin A, a flavone from the medicinal plant *Scutellaria baicalensis* and the tree *Oroxylum indicum*, also increases BDNF production by activation of the ERK/CREB signaling pathway in rat primary cortical neurons (Jeon et al., 2011). It was also shown that ERK1/ERK2 activation mediates neurite outgrowth induced by honokiol (a lignin isolated from Magnolia trees) in primary rat cortical neurons (Zhai et al., 2005). We found that curcumin stimulates the proliferation of neural progenitor cells and adult hippocampal neurogenesis by a mechanism involving ERK activation (Kim et al., 2008). Moreover, the citrus flavonoid heptamethoxyflavone increased BDNF production and neurogenesis in the hippocampus after cerebral global ischemia in mice (Okuyama et al., 2012). Although several different phytochemicals can stimulate ERK1/ERK2 activation to promote neuronal survival, neurite outgrowth, and neurogenesis, in no case has the molecular mechanism by which the phytochemicals activate ERKs been established. Although direct interactions with the ERKs have not yet been ruled out, less specific mechanisms involving induction of mild cellular stress are perhaps as likely or more likely.

In contrast with the ERK1/ERK2 pathway that promotes cell survival and growth, the activation of p38 MAPK and JNK pathways often triggers programmed cell death (Harper and LoGrasso, 2001). Both p38 MAPK and JNK signaling pathways are activated by a variety of environmental or cellular stress stimuli, including inflammatory cytokines, UV irradiation, heat shock, osmotic shock, and DNA-damaging agents. JNK and p38 play a critical role in the "decision" of neurons to undergo apoptosis, perhaps to avoid dying by necrosis (Harper and LoGrasso, 2001; Malemud, 2007; Huang et al., 2009). Activation of p38 MAPK and JNK signaling pathways was proposed to explain antiproliferative and proapoptotic effects of natural phytochemicals in cancer cells. For example, EGCG induced apoptotic cell death in HT-29 human colon cancer cells through JNK activation (Chen et al., 2003). The flavonoid isoorientin decreased cell viability in HepG2 cells in a dose- and time-dependent manner by induction of apoptosis, which involved suppression of ERK1/ERK2 and activation of JNK and p38 MAPK (Yuan et al., 2013). Similarly, 2′-nitroflavone induced apoptosis in hematologic cancer cells and activated p38 MAPK and JNK but decreased phosphorylation levels of ERK1/ERK2 (Cárdenas et al., 2012). Luteolin, a dietary flavonoid, triggered apoptosis in Neuro-2a mouse neuroblastoma cells through endoplasmic reticulum stress and mitochondrial membrane permeability transition, which are mediated by activation of JNK and p38 MAPK (Choi et al., 2011). EGCG-induced apoptosis was mediated by p38 MAPK and JNK activation in chondrosarcoma cells (Yang et al., 2011b). Anticancer effects of trichostatin were potentiated by curcumin treatment in breast cancer cells, and it was proposed that apoptosis induced by a combination of curcumin and trichostatin involves JNK activation (Yan et al., 2013). Likewise, it was shown that JNK pathways are

TABLE 7
Phytochemicals that modify MAPK signaling

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
EGCG	Cervical cells	Increase p53, p21(WAF-1), and p27(KIP-1) levels, reduce cyclin E level, and reduced CDK2 kinase activity	Inhibited EGFR-dependent activation of the MAPKs ERK1/ERK2	Sah et al. (2004)
	MCF10A cell line, MDA-MB-231 cell line	Inhibitory effect toward HGF/Met signaling	Repressed ERK phosphorylation	Bigelow and Cardelli (2006)
	DU145 cells	Prevent phosphorylation of tyrosine 1234/1235	Reduced the HGF-induced phosphorylation of ERK	Duhon et al. (2010)
	ARO cells	Inhibit the growth of the cells	Suppressed phosphorylation of ERK1/ERK2, JNK, and p38	Lim and Cha (2011)
	RLE cells	Inhibit gap junctional intercellular communication and phosphorylation of Cx43	Phosphorylation of ERK1/ERK2	Kang et al. (2008b)
	PC-3 cell	Inhibit the cell proliferation	Activation ERK1/ERK2 pathway	Albrecht et al. (2008)
	NHBE cells	Downregulation of NF-κB-regulated proteins cyclin D1	Inhibited phosphorylation of ERK1/ERK2, JNK, and p38 MAPKs	Syed et al. (2007)
	HT-29, HCA-7 cell line	Inhibit NF-κB, decreased COX-2 promoter activity	Downregulated the ERK1/ERK2	Peng et al. (2006)
	DU145, LNCaP cells	Decrease the levels of PI3K and p-Akt	Increase ERK1/ERK2	Siddiqui et al. (2004)
Polyphenon E, caffeine	Female A/J mice	Inhibit cell proliferation	Lowered levels of c-Jun and Erk 1/Erk2 phosphorylation	Lu et al. (2006)
6-ME)	HUVECs	Inhibit angiogenesis and suppress tumor growth	Inhibited VEGF-induced phosphorylation of ERK1/ERK2 MAPK	Bellou et al. (2012)
Resveratrol	EBV-positive BL cells	Arrest cell cycle progression in G(1) phase	Induction of p38 MAPK phosphorylation and suppression of ERK1/ERK2 signaling pathway	De Leo et al. (2011)
	MCF-7 cells	Lead to apoptosis	Inhibited activation of ERK1/ERK2	Lin et al. (2006)
	A375 cell line	Inhibit growth and induce apoptosis	Induced phosphorylation of ERK1/ERK2	Niles et al. (2003)
	THP-1 cells	Inhibit LPS-induced IL-8 production	inhibited ERK and p38 MAPK phosphorylation	Oh et al. (2009)
Curcumin	Hepatic stellate cells	Abrogate the membrane translocation of GLUT2 and suppress GLUT2 expression	Interrupting the p38 MAPK signaling pathway abrogate the membrane translocation	Lin and Chen (2011)
	B16 cells (melanoma)	Inhibit melanin synthesis and cellular tyrosinase activity	Activation of ERK and p38 MAPK	Tu et al. (2012)
	3T3-L1 cells	Restore nuclear translocation of β-catenin	Inhibited ERK, JNK, and p38	Ahn et al. (2010)
Chalcones	A549 cells	Induce cytotoxicity and inhibit NF-κB	Activation of ERK1/ERK2 and JNK	Warmka et al. (2012)
Sappanchalcone	Oral cancer cells	Suppress the cells growth and induce apoptosis	Activation of p38, ERK, and JNK	Lee et al. (2011b)
Butein (3,4,2′,4′-tetrahydroxychalcone)	MDA-MB-231 cells	Inhibit the proliferation of breast cancer cell and promote apoptosis	Decreased the phosphorylation of ERK, increased p38 activity	Yang et al. (2012)
Extra virgin olive oil	HER2-gene amplified JIMT-1 cell line	Inhibit mitosis to promote G2/M cell cycle arrest	Activated the p38 MAPK	Oliveras-Ferraros et al. (2011)
Fisetin	HeLa cells	Reduce tumor growth and induce apoptosis	Activation of the phosphorylation of ERK1/ERK2	Ying et al. (2012)
Genistein	Caco-2 cells	Increase Nrf2 mRNA and protein expression	Activated the ERK1/ERK2	Zhai et al. (2013)
Grape seed procyanidin	A2780/T cells	Inhibit P-gp expression	Inhibited MAPK/ERK pathway	Zhao et al. (2013a)
Hydroxytyrosol	Human colon adenocarcinoma cells	Block cell cycle G2/M	Strong inhibition of ERK1/ERK2	Corona et al. (2009)
Kaempferol	U-2 OS cells	Inhibit metastasis of cells	Attenuated the MAPK signaling pathway	Chen et al. (2013)
Myricetin	T24 cells	Lead to G2/M cell cycle arrest and induce apoptosis	Phosphorylation of p38 MAPK	Sun et al. (2012)
Red ginseng essential oil	HepG2 cells	Diminish oxidative stress and restore the activity and expression of SOD, catalase, GPx	Inhibited the phosphorylation of upstream MAPKs	Bak et al. (2012a)
Hesperetin	Postmitotic neuron cells	Partially reverse staurosporine-induced cell death	Increases in the level of ERK1/ERK2 phosphorylation	Rainey-Smith et al. (2008)
	Cortical neurons	Prevent neuronal apoptosis	Activation of both Akt and ERK1/ERK2	Vauzour et al. (2007)

(*continued*)

TABLE 7—*Continued*

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
L-Theanine	SH-SY5Y cells	Attenuate both rotenone- and dieldrin-induced DNA fragmentation and apoptotic death	Rotenone- and dieldrin-induced downregulation of ERK1/ERK2 phosphorylation	Cho et al. (2008)
Resveratrol	Rat primary astroglia	Increase BDNF and GDNF production	Induced the phosphorylation of ERK1/ERK2	Zhang et al. (2012a)
Oroxylin A	Rat cortical neurons	Increase BDNF production	Activated ERK1/ERK2 MAPK	Jeon et al. (2011)
Honokiol	Rat cortical neurons	Neurite outgrowth	ERK1/ERK2 activation	Zhai et al. (2005)
Curcumin	Neural progenitor cells	Promote cell proliferation and adult hippocampal neurogenesis	Activated ERK and p38 kinases	Kim et al. (2008)
Heptamethoxyflavone	Transient global ischemia mouse	Increase BDNF and neurogenesis	Induced the phosphorylation of ERK1/ERK2	Okuyama et al. (2012)
Calycopterin	PC12 cells	Inhibit H_2O_2-induced nuclear translocation of NF-κB	Suppressed ERK, JNK, and p38 MAPK phosphorylation	Farimani et al. (2011)
Koshu (grape seed extract)	Neonatal mouse hippocampal neurons	Neuroprotective effects against excitotoxicity	Inactivation of ERK1/ERK2	Narita et al. (2011)
Mollugin	Mouse hippocampal HT22 cell line, BV2 cells	Increase expression of HO1, activate HO	Activated the p38 MAPK pathway	Jeong et al. (2011)
EGCG	HT-29 cells	Induce apoptotic cell death	Inhibition of JNK pathway	Chen et al. (2003)
	Human chondrosarcoma cells	Induce apoptosis	Induced p38 and JNK phosphorylation	Yang et al. (2011b)
Isoorientin	HepG2 cells	Induce mitochondria-mediated apoptosis	Suppressed ERK1/ERK2, and activation of JNK and p38 MAPK	Yuan et al. (2013)
Luteolin	Neuro-2a mouse neuroblastoma cells	Induce apoptosis through ER stress and mitochondrial dysfunction	Activation of JNK, p38, and ERK	Choi et al. (2011)
Curcumin, tricostatin A	Breast cancer cells	Decrease cell viability	Increased phosphorylated JNK and phosphorylated p38	Yan et al. (2013)
Resveratrol	JB6 mouse epidermal cell line	Induce p53 activation and induce apoptosis	Activated JNKs	She et al. (2002)
Quercetin	HepG2 cells	Induce cell death	Activation of the JNK pathway	Granado-Serrano et al. (2010)
Baicalein	HT22 cells	Reduce endoplasmic reticulum stress–induced apoptosis	Modulated the endoplasmic reticulum stress-mediated activation of p38 MAPK and JNK pathways	Choi et al. (2010)
Luteolin	Rat cortical neurons	Neuroprotective effect	Protective mechanism is mediated by preventing of p38 MAPK and JNK pathways and caspase-3 activations	Cheng et al. (2010)
Oxyresveratrol	SH-SY5Y cells	Neuroprotective effects against PD	Attenuated 6-OHDA–induced phosphorylation of JNK and c-Jun	Chao et al. (2008)
Curcumin	PD mouse model	Improve behavioral deficits and prevent dopaminergic neuronal death	Inhibited MPTP/MPP (+)-induced phosphorylation of JNK1/JNK2	Yu et al. (2010b)
Apigenin	BV-2 cell line	Inhibit the production of NO and prostaglandin E_2	Suppressed p38 MAPK, JNK phosphorylation	Ha et al. (2008)

6-ME, 6-methoxyequol; CDK, cyclin-dependent kinase; EBV, Epstein–Barr virus; EGFR, epidermal growth factor receptor; GLUT, glucose transporter; HGF, hepatocyte growth factor; P-gp, P-glycoprotein.

involved in resveratrol-induced p53 activation and induction of apoptosis in the JB6 mouse epidermal cells (She et al., 2002).

Whereas some phytochemicals activate JNK and p38 MAPKs to trigger death of cancer cells, phytochemicals can also promote survival of neurons and suppress neuroinflammation by inhibiting these MAPKs. The flavone scutellarin suppressed LPS-induced activation of microglial cells by inhibiting JNK and p38 MAPK activation without affecting the activity of ERK (Wang et al., 2011d). Anti-inflammatory effects of the flavonoid icariin in microglia are also mediated by suppression of JNK/p38 MAPK pathways (Zeng et al., 2010). Baicalein reduced endoplasmic reticulum stress–induced p38 MAPK and JNK pathways and apoptosis in murine hippocampal neuronal cells (Choi et al., 2010). Inhibition of JNK and p38 MAPK mediates the protective action of luteolin against Aβ in rat cortical neurons, a model relevant to AD (Cheng et al., 2010). Resveratrol and its derivatives were shown to have protective effects against 6-OHDA–induced neurotoxicity in human neuroblastoma cells, and attenuated the phosphorylation of JNK and c-Jun triggered by 6-OHDA (Chao et al., 2008, 2010). Curcumin treatment ameliorated behavioral deficits and prevented dopaminergic neuronal death in a mouse PD model. Moreover, curcumin effectively inhibited MPTP/MPP^+-induced phosphorylation of JNK1/JNK2 in vivo (Yu et al.,

2010b). Although the mechanisms by which phytochemicals differentially modify the activation states of ERK1/ERK2, JNKs, and p38 MAPKs remain to be clarified, the available evidence does suggest the therapeutic potential of phytochemicals in neuroinflammatory and neurodegenerative disorders.

4. Glycogen Synthase Kinase-3β. GSK-3 is a serine-threonine kinase that was initially named for its ability to phosphorylate and inactivate glycogen synthase. In mammals, there are two highly homologous forms of GSK-3: GSK-3α and GSK-3β. Mice lacking GSK-3β die during embryonic development or as neonates, whereas no significant abnormalities are evident in GSK-3α knockout mice (Hoeflich et al., 2000; MacAulay et al., 2007). GSK-3β is involved in signaling pathways that regulate cellular bioenergetics, proliferation, migration, apoptosis, inflammation, and immune responses. Since GSK-3β has been implicated in glucose homeostasis, including the phosphorylation of insulin receptor substrate (IRS)-1 and of the gluconeogenic enzymes, GSK-3β inhibitors have therapeutic potential for treating type 2 diabetes (Lochhead et al., 2001). Several phytochemicals can inhibit GSK-3β activity (Table 8). The beneficial effects of EGCG against the metabolic syndrome are mediated, in part, by GSK-3β inhibition, which enhances insulin sensitivity and activates enzymes involved in glycogen synthesis and lipogenesis (Kim et al., 2013b). Administration of green tea polyphenols decreases GSK-3β and the detrimental effects of a high-fructose diet on insulin signaling, lipid metabolism, and inflammation in the cardiac muscle of rats (Qin et al., 2010). It was reported that the antiadipogenic activity of *Citrus aurantium* flavonoids was mediated by the inhibition of GSK-3β phosphorylation (Kim et al., 2012).

Recent findings suggest that GSK-3β plays an important role in regulating inflammatory processes. GSK-3β participates in a number of signaling pathways in the immune response that promote the production of inflammatory molecules and cell migration. GSK-3β inactivation can suppress inflammation by increasing anti-inflammatory cytokine production while concurrently suppressing the production of pro-inflammatory cytokines (Jope et al., 2007; Wang et al., 2011a). Although there are several studies reporting that phytochemicals were effective to reduce proinflammatory cytokines and GSK-3β expression, the data are not sufficient to conclude that anti-inflammatory properties of phytochemicals are directly mediated through GSK-3β inhibition (Ahn et al., 2010; Qin et al., 2010).

GSK-3β is involved in signaling pathways that affect cell proliferation and apoptosis. A prominent substrate of GSK-3β is β-catenin, a key protein in the canonical Wnt signaling pathway that regulates cell proliferation. GSK-3β also participates in a number of apoptotic signaling pathways by phosphorylating transcription factors that regulate apoptosis; GSK-3β acts as a tumor suppressor in some cancers while potentiating growth of others (Jope et al., 2007; Mills et al., 2011). GSK-3β inhibitors effectively induced apoptosis in pancreatic cancer and glioma cells (Kotliarova et al., 2008; Marchand et al., 2012). Ellagic acid, a plant-derived polyphenol, induced apoptosis in an animal model of oral oncogenesis by preventing the constitutive activation of Wnt pathway through downregulation of Fz, Dvl-2, GSK-3β, and nuclear translocation of β-catenin (Anitha et al., 2013). Black tea polyphenols substantially reduced IGF-I–mediated growth of prostate cancer cells by decreasing downstream effects of Akt activation including phosphorylation of GSK-3β (Klein and Fischer, 2002). EGCG reduced the viability of human skin cancer cells, and its cytotoxic effects were associated with inactivation of β-catenin signaling (Singh and Katiyar, 2013).

Recent findings suggest that GSK-3β plays important roles in the pathogenesis of neurodegenerative and psychiatric disorders. GSK-3β is relatively abundant in the adult brain (Woodgett, 1990; Grimes and Jope, 2001). Lithium, an inhibitor of GSK-3β, has been shown to have therapeutic potential in several neurologic disorders and indeed is widely prescribed to patients with bipolar disorder (Chiu et al., 2013). Because it phosphorylates τ and may contribute to the formation of neurofibrillary tangles, GSK-3β is also a potential target for AD. Puerarin, an isoflavone glycoside from Kudzu root (*Pueraria lobata*), protected primary hippocampal neurons against Aβ-induced stress by inhibiting GSK-3β signaling (Zou et al., 2013). Pretreatment with (±)-catechin protected dopaminergic neurons against MPTP-induced death in mice by a mechanism involving inhibition of GSK-3β (Ruan et al., 2009). The citrus bioflavonoid luteolin reduced Aβ generation in "Swedish" mutant APP transgene-bearing neuron-like cells and primary neurons, and diosmin (a semishynthetic drug modified from hesperidin) significantly reduced Aβ pathology, reduced GSK-3 activity, and disrupted the association of presenilin 1 with APP (Rezai-Zadeh et al., 2009). In addition, EGCG prevented oxidative stress–induced death of motor neurons expressing a mutant form of SOD1 that causes ALS, by activating PI3K/Akt and inhibiting GSK-3β (Koh et al., 2004)

Studies relevant to AD have shown that GSK-3β activity promotes Aβ production and that GSK-3β directly phosphorylates τ, resulting in the formation of neurofibrillary tangle-like filaments (Alonso et al., 2001). Abnormal increases of GSK-3β levels and activity occur in brain cells of patients with AD, and are associated with neuronal death, τ pathologies, and a decline in cognitive function (Bhat et al., 2004). Therefore, the identification and characterization of GSK-3β inhibitors is an active area of investigation in the AD research field (Bhat et al., 2004; Hooper et al., 2008; Gao et al., 2012). The *bis*-indole indirubin, an active

TABLE 8
Phytochemicals that modify GSK-3β signaling

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
EGCG	HepG2 cells	Inhibit lipogenesis	Metabolic syndrome were mediated by GSK-3β inhibition	Kim et al. (2013b)
Green tea polyphenols	Cardiac muscle in insulin-resistant rats	Reduce detrimental effects of a high-fructose diet on insulin signaling, lipid metabolism, and inflammation	Decreased GSK-3β	Qin et al. (2010)
Citrus aurantium flavonoids	3T3-L1 cells	Inhibit adipogenesis	Mediated by the inhibition of GSK-3β phosphorylation	Kim et al. (2012)
Curcumin	3T3-L1 cells	Inhibit adipogenic differentiation	Reduced differentiation-stimulated expression of GSK-3β	Ahn et al. (2010)
Ellagic acid	Hamster buccal pouch carcinogenesis model	Induce apoptosis	Preventing the constitutive activation of Wnt pathway through downregulation of GSK-3β	Anitha et al. (2013)
Black tea polyphenols	PrEC and Du145 prostate carcinoma cells	Inhibit IGF-I–mediated prostate cancer incidence	Decreased downstream effects of Akt activation including phosphorylation of GSK-3β	Klein and Fischer (2002)
EGCG	Human skin cancer cell line	Reduce cell viability and increased cell death	Reduced phosphorylation of GSK-3β	Singh and Katiyar (2013)
3,3′-Diindolylmethane	VSMC neointima formation in a carotid injury model	G_0/G_1 phase cell cycle arrest, inhibit infiltration of inflammatory cell	Activities of downstream signaling molecules including GSK-3β	Guan et al. (2012)
	Oral squamous cell carcinoma	Suppress the viability of the cells by inducing apoptosis and G2/M arrest	Inhibit downstream effectors of the GSK-3β	Weng et al. (2012)
Genistein	PC3 cells	Decrease expression of β-catenin	Increased GSK-3	Liss et al. (2010)
Nimbolide	HepG2 cells	Abrogate canonical NF-κB and Wnt signaling to induce caspase-dependent apoptosis	Apoptosis evasion by evaluating members of GSK-3β	Kavitha et al. (2012)
Quercetin	BEAS-2B cells	Decrease the viability of the cells via apoptosis	Inactivated GSK-3β	Lee and Yoo (2013)
Puerarin	Primary hippocampal neurons	Neuroprotection against Aβ	Inhibited GSK-3β signaling	Zou et al. (2013)
(±)-Catechin	Mice	Protect dopaminergic neurons	Modulate the rapid activation of GSK-3β against MPTP-induced dopaminergic neurotoxicity	Ruan et al. (2009)
Luteolin	"Swedish" mutant APP transgene-bearing neuron-like cells and primary neurons	Significantly reduce Aβ pathology and disrupt PS1-APP association	Reduced GSK-3 activity	Rezai-Zadeh et al. (2009)
EGCG	Mutant hSOD1 gene (G93A) motoneuron cells	Prevent oxidative stress–induced death	Inhibition of GSK-3β	Koh et al. (2004)
bis-Indole indirubin	Sf9 cells	Inhibit τ phosphorylation at AD-specific sites	Powerful GSK-3β inhibitor	Leclerc et al. (2001)
Morin	Hippocampus of 3xTg-AD mice	Block GSK-3β–induced τ phosphorylation, and attenuate τ hyperphosphorylation in 3xTG-AD mice	Inhibited GSK-3β activity	Gong et al. (2011)

3xTg-AD, triple transgenic AD; PS1, presenilin 1; VSMC, vascular smooth muscle cell.

ingredient of traditional Chinese medicines, was reported to be a powerful GSK-3β inhibitor that prevents τ phosphorylation at AD-specific sites (Leclerc et al., 2001). A structure–activity relationship study suggested that indirubins bind to the ATP-binding pocket of GSK-3β in a manner similar to their binding to cyclin-dependent kinases (Bertrand et al., 2003; Polychronopoulos et al., 2004). We previously reported that the flavonol morin effectively inhibited GSK-3β activity and blocked GSK-3β–induced τ phosphorylation in vitro, and attenuated τ hyperphosphorylation and paired helical filament-like immunoreactivity in hippocampus of triple transgenic AD mice in vivo (Gong et al., 2011). A pharmacophore model based on a computational approach revealed that morin has high potential complementarity to fit into the ATP-binding pocket of GSK-3β (J. Lee and D. Park, unpublished data). Although many phytochemicals were shown to have antidepressant effects, there are few studies of the application of phytochemicals to bipolar disorder. One study proposed that baicalin is a new prodrug inhibitor of prolyl oligopeptidase, which has been associated with schizophrenia, bipolar affective disorder, and related neuropsychiatric disorders (Tarragó et al., 2008). Given the established efficacy of lithium for bipolar disorder, phytochemicals that inhibit GSK-3β

would be attractive candidate interventions for this disorder.

5. Insulin Signaling. The insulin signaling pathway controls blood glucose levels by stimulating the transport of glucose into muscle, liver, and other insulin-responsive cells, and by inhibiting gluconeogenesis. Insulin binds to the extracellular α-subunits of the insulin receptor causing a conformational change in the insulin receptor, a transmembrane glycoprotein with intrinsic tyrosine kinase activity. The activated receptor stimulates the phosphorylation of the receptor itself and downstream substrates (Fig. 6), including IRS-1. Rather than have a direct interaction with SH2 proteins, insulin receptors propagate the signal through IRS-1 on multiple tyrosine residues, which in turn recognize and bind to the SH2 domains in signal transduction proteins, including PI3K, growth factor receptor bound protein 2/son of sevenless homolog 1 ($p21^{ras}$ pathway), and SH/protein tyrosine phosphatase 2 (tyrosine phosphatase pathway) (White and Kahn, 1994).

Insulin signaling responds dynamically and adaptively to metabolic states, including feeding, fasting, exercise, and stress. Disturbances of insulin signaling occur in several pathologic conditions, including type 1 diabetes (insulin deficiency), type 2 diabetes (insulin resistance), and the metabolic syndrome. A sedentary gluttonous lifestyle promotes the metabolic syndrome and type 2 diabetes that, in turn, increase the risk of cardiovascular disease, stroke, obesity, cancers, and AD. Several phytochemicals exhibit antidiabetic actions (Table 9). Several dietary flavonoids can improve pancreatic β-cell function and insulin secretion, and can increase the insulin sensitivity of muscle, liver, and fat cells (Babu et al., 2013). Curcumin improved insulin resistance in skeletal muscle of diabetic rats induced by a high-fat diet plus streptozotocin administration (Na et al., 2011). Curcumin improved insulin resistance and glucose tolerance in type 2 diabetic *db/db* mice but not in nondiabetic *db/+* mice (Seo et al., 2008). Green tea extract containing EGCG markedly improved glucose tolerance and increased glucose-stimulated insulin secretion by preserving islet structure in diabetic *db/db* (leptin receptor mutant) mice (Wolfram et al., 2006; Ortsäter et al., 2012). The natural flavonoids quercitrin, quercetin, and genistein attenuated hyperglycemia and increased insulin sensitivity in a mouse model of diabetes (Lee, 2006; Kobori et al., 2009; Babujanarthanam et al., 2010).

Beneficial properties of dietary phytochemicals were also shown in diet-induced obesity and metabolic syndrome in animal and human studies, probably by enhancing insulin production and insulin sensitivity (Panickar, 2013). Resveratrol treatment ameliorates abnormal insulin secretion and morphologic changes of pancreatic β cells in mice fed a high-fat diet and improves insulin resistance in rats fed fructose and in mice on a high-calorie diet (Baur et al., 2006; Bagul et al., 2012; Zhang et al., 2012a). A recent study showed that dietary supplementation with resveratrol increases insulin sensitivity and improves glucose tolerance in a nonhuman primate, the gray mouse lemur (*Microcebus murinus*) (Marchal et al., 2012). Curcumin treatment was evaluated in mice fed a high-fat diet and was shown to prevent insulin resistance and obesity by attenuating lipogenic gene expression in the liver and inflammatory responses in adipose tissue (Shao et al., 2012). Beneficial effects of EGCG were demonstrated in a model of Western diet–induced insulin resistance (Bose et al., 2008; Chen et al., 2009b, 2011b). Although these studies suggest that some phytochemicals can reverse insulin resistance and enhance insulin signaling, the molecular mechanisms have not been established.

Insulin-sensitizing properties of phytochemicals may involve IGFs. In rat models of diabetes, curcumin restored IGF-I signaling and ameliorated a learning and memory deficit (Isik et al., 2009). In another study, green tea polyphenols decreased serum IGF-I and leptin levels in a model of diet-induced obesity, which is consistent with an enhancement of IGF-1 and leptin sensitivity (Shen et al., 2012). IGF-I affects cells in complex ways that are tissue specific. Although IGF-I acts as a neurotrophic factor and is generally considered beneficial for the brain, it can cause skeletal muscle hypertrophy and cancer cell proliferation. Increased soy consumption was associated with elevated circulating levels of IGF-I in postmenopausal women at high risk for developing breast cancer, indicating the increased risk for cancer growth (McLaughlin et al., 2011). By contrast, repeated doses of resveratrol reduced levels of IGF-I in healthy volunteers, suggesting a potential for resveratrol in cancer prevention (Brown et al., 2010). Because both soy isoflavones and resveratrol can improve insulin sensitivity in models of diabetes and metabolic disorders, differential regulation of IGF-I signaling might contribute to the different effects of these polyphenols on proliferative cells.

Insulin/IGF-1–like receptor signaling pathways have a strong influence on aging processes in organisms ranging from worms and flies to humans (Apfeld and Kenyon, 1998; Barbieri et al., 2003; Barzilai and Bartke, 2009). Studies have shown that dietary phytochemicals can extend the lifespan in worms and flies by mechanisms involving modulation of insulin-like signaling and upregulation of adaptive stress response pathways. For example, *C. elegans* fed blueberry polyphenols exhibit an extended lifespan and are more resistant to heat stress (Wilson et al., 2006). The life span of worms is also extended by dietary resveratrol, by a mechanism requiring AMP-activated protein kinase (Greer and Brunet, 2009). In the nervous system, IGF-I plays important roles in neurogenesis, synaptic plasticity, and neuronal survival and is neuroprotective in a range of

TABLE 9
Phytochemicals that modify insulin signaling

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
Curcumin	Skeletal muscle of diabetic rats	Improve insulin resistance	Mediated through LKB1-AMPK	Na et al. (2011)
Epicatechin gallate	*db*/*db* mice	Reduce the number of pathologically changed islets of Langerhans and increase the number and the size of islets	Enhanced glucose tolerance and glucose-stimulated insulin secretion	Ortsäter et al. (2012)
	db/*db* mice	Increase glucokinase mRNA expression in the liver	Enhanced glucose tolerance and glucose-stimulated insulin secretion	Wolfram et al. (2006)
Quecitrin and quercetin	Diabetic rats	Exhibit a protective role on the pancreatic islets	Increased insulin sensitivity	Babujanarthanam et al. (2010)
	Diabetic mice	Improve liver and pancreas functions by enabling the recovery of cell proliferation	Increased insulin sensitivity through the inhibition of Cdkn1a expression	Kobori et al. (2009)
Genistein	Diabetic mice	Increase blood glucose, antioxidant enzyme activities, and lipid profile	Increased insulin sensitivity	Lee (2006)
Resveratrol	Caucasian (blood)	Improve insulin sensitivity and decrease insulin resistance	Decreased oxidative stress and more efficient insulin signaling via the Akt pathway	Brasnyó et al. (2011)
Piceatannol	*db*/*db* mice	Antidiabetic effect	Improved glucose tolerance	Minakawa et al. (2012)
Bilberry anthocyanins		Enhance insulin sensitivity	Increased AMPK phosphorylation	Takikawa et al. (2010)
Hesperidin and naringin	*db*/*db* mice	PEPCK and G6Pase expression	Increased plasma insulin	Jung et al. (2004)
Epicatechin gallate	C2C12 mouse skeletal muscle cell	Antiobesity and anti-type 2 diabetes mellitus	Attenuated insulin resistance	Deng et al. (2012)
Flavonoid composition of cranberry extract	Liver and muscle (mice)	Downregulation of the hepatic cholesterol synthesis pathway	Amelioration of insulin resistance	Shabrova et al. (2011)
Troxerutin	Hippocampus (mice)	A possible candidate for the prevention and therapy of cognitive deficits in T2D	Enhanced insulin signaling pathway	Lu et al. (2011)
Resveratrol	High-fat diet–fed mice	Protect islets from abnormal insulin secretion	Promoted the expression of SIRT1 in islets and Bcl-2/Bax and levels of malondialdehyde/glutathione peroxidase	Zhang et al. (2012b)
	Fructose-fed rats	Increase nuclear level of NRF2	Attenuated insulin resistance	Bagul et al. (2012)
	High-fat diet–fed mice	Produce changes associated with longer lifespan	Increased insulin sensitivity, reduced insulin-like growth factor-1	Baur et al. (2006)
	Gray mouse lemurs	Beneficial effects on metabolic alterations	Increased insulin sensitivity by improving the glucose tolerance	Marchal et al. (2012)
Curcumin	High-fat diet–fed mice	Inhibit lipogenic gene expression in the liver and blocked and the inflammatory response in the adipose tissue	Induced insulin resistance	Shao et al. (2012)
Epicatechin gallate	High-fat diet–fed mice	Attenuate levels of plasma cholesterol, MCP-1, CRP, IL-6, and GCSF	Improved glucose tolerance Insulin resistance	Chen et al. (2011b)
	High-fat diet–fed rats	Increase markers of thermogenesis and differentiation in adipose tissue	Increased glucose tolerance	Chen et al. (2009b)
	High-fat diet–fed rats	Decrease liver weight, liver triglycerides, and mesenteric fat weight and blood glucose compared with high-fat–fed control mice	Attenuated insulin resistance	Bose et al. (2008)
Cinnamon	Mouse 3T3-L1 preadipocyte	Regulate the expression of multiple genes in adipocytes	Increased insulin signaling	Cao et al. (2010)
Resveratrol	HC-fed mice	Reduce IGF-I levels/increased AMPK, PGC-1α activity, and mitochondrial number	Increased insulin sensitivity, reduced IGF-1	Baur et al. (2006)
	Adipocyte (HF-rat)	Improve the metabolic profile of HF-fed offspring born from pregnancies complicated by IUGR	Ameliorated insulin resistance and glucose intolerance	Dolinsky et al. (2011)
Flavonoid compounds isolated from *Hyphaene thebaica* epicarp	Rat	Antidiabetic effects	Improved glucose and insulin tolerance	Salib et al. (2013)

(*continued*)

TABLE 9—*Continued*

Phytochemical	Target Tissue/Cells	Effects	Involved Molecular Mechanism	Reference
Tetrahydro iso-α acids	High-fat diet–fed mice	Antidiabetic effects	Increased insulin sensitivity	Everard et al. (2012)
Purple corn color anthocyanidin	T2D mice	Lipogenic gene expression	Increased serum insulin level	Roy et al. (2008)
Cyanidin-3-glucoside	*db*/*db* mice and HF-fed obese mice	Phosphorylation of Akt, FOXO1	Improved insulin sensitivity	Guo et al. (2012)

AMPK, AMP-activated protein kinase; GCSF, granulocyte cell-stimulating factor; HC, high calorie; HF, high fat; IL, interleukin; IUGR, intrauterine growth restriction; LKB-1, liver kinase B1; MCP, monocyte chemotactic protein; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, PPARγ coactivator 1α; T2D, type 2 diabetes mellitus.

models of neuronal degeneration (Anlar et al., 1999; Aberg et al., 2000; Torres-Aleman, 2000). Interestingly, in the Avon longitudinal study of parents and children, IGF-I levels in serum were positively associated with the intelligence quotient in children aged 8 to 9 years (Gunnell et al., 2005). Since IGF-I levels can be altered by diet and other environmental factors, the authors of the latter study proposed that IGF-1 may mediate effects of the childhood environment on their brain development. Dietary phytochemicals can affect IGF-1 signaling and cognitive function. For example, short-term blueberry supplementation stimulated hippocampal neurogenesis and ameliorated memory deficits in aged rats by a mechanism involving increased IGF-1 and IGF-1 receptor levels (Casadesus et al., 2004).

FOXO transcription factors are negatively regulated by the insulin/IGF-1 signaling pathway and have been postulated to play important roles in apoptosis, cell cycle regulation, energy metabolism, and oxidative stress resistance. Only one FOXO gene was identified in invertebrates (which is termed *daf-16* in the nematode *C. elegans* and *dFOXO* in the fruit fly), whereas mammals have four FOXO genes (FOXO1, FOXO3, FOXO4, and FOXO6). It is well known that daf-16 and dFOXO are associated with longevity in the nematode and the fruitfly, respectively (Greer and Brunet, 2005). Although mammalian FOXO is also negatively regulated by Akt in response to insulin/IGF stimulation, the life-prolonging effect of FOXO appears to be minimal. Rather, it was proposed that the antineoplastic effect of dietary restriction is mediated by FOXO1 (Yamaza et al., 2010). The activity of FOXO proteins is regulated by several post-translational modifications, including phosphorylation, acetylation, and methylation. Several studies suggest the involvement of FOXO in age-related neurodegenerative diseases. FOXO reduces the toxicity associated with aggregation-prone proteins involved in AD and HD (Morley et al., 2002; Cohen et al., 2006; Parker et al., 2012). Interestingly, it was proposed that the FOXO responses to oxidative stress are involved in both insulin resistance and AD pathogenesis, and thus FOXO could be a potential molecular target for these disorders (Manolopoulos et al., 2010). Therefore, there is a possibility that phytochemicals could alter FOXO activity either through directly interacting with FOXO or indirectly modulating the regulatory enzymes involved in FOXO post-translational modifications. Taken together, the available data suggest that phytochemicals that modify the insulin/IGF-I/FOXO signaling pathway have therapeutic potential for metabolic and neurodegenerative disorders.

VII. Phytochemical-Centric Computational Drug Discovery and Design

One approach to phytochemical-based drug discovery is to develop screens for activation of a specific adaptive stress response pathway and then perform medicinal chemistry around lead phytochemicals emerging from the screen. Here is one example of such an approach. A book entitled *Insect Antifeedants* by Koul (2005) caught the attention of one of the authors (M.P.M.) in 2009. The book includes >700 phytochemicals that have been isolated from a range of plant species and are shown to exert noxious effects on insects, in many cases at concentrations that the pests might be exposed to in their natural environment. Because the nervous system (e.g., taste receptors and olfactory neurons) is particularly important for sensing and responding to potentially toxic chemicals, it seemed likely that some of the "natural pesticides" would activate one or more adaptive cellular stress response signaling pathways in neurons. To test this hypothesis, a panel of phytochemicals was selected from Koul's (2005) compendium of insect antifeedants that included a diverse array of structures and botanical sources. Luciferase reporter cell assays were used to identify phytochemicals in the panel that could, at sublethal concentrations, activate one or more of three prominent stress responsive transcription factors: Nrf-2, NF-κB, and FOXO. The screen resulted in several hits, and one naphthoquinone from the genus *Plumbago* (plumbagin) was demonstrated to induce a 15-fold increase in Nrf-2 transcriptional activity and exhibited neuroprotective activity in a mouse model of stroke (Son et al., 2010). Analogs of plumbagin were synthesized and screened and several demonstrated exhibited neuroprotective activity (Choi et al., 2012; Son et al., 2013) and extended lifespan in *C. elegans* by a hormetic mechanism (Hunt et al., 2011). This provides a proof-of-principle example for the approach of developing phytochemical "toxins" as potential therapeutic agents. In the remainder of this section, we

describe a different approach to phytochemical-based drug discovery that utilizes molecular modeling.

A. Docking Simulation. Computational drug discovery and design, particularly in silico structure-based drug design, can provide valuable contributions in hit- and lead-compound discovery (Kuntz, 1992). Advanced computer-based techniques can assist in both the discovery and optimization of lead compounds (Jorgensen, 2004). Among computer-based techniques for drug discovery and design, docking simulation and pharmacophore analysis are regarded as the most successful tools for elucidating molecular interactions between small molecules and macromolecules (Cavasotto and Orry, 2007). These applications provide valuable starting points for establishing molecular targets of phytochemicals as a complement to high-throughput screening of large compound collections. The approaches are helpful in understanding how phytochemicals perturb cellular stress pathways by modeling their interactions with their target proteins (Lee et al., 2011a).

Docking simulation approaches use specialized computer programs to find novel enzyme inhibitors and other therapeutic agents in drug development stages. The docking process involves the prediction of small molecule conformation and positioning within the pocket of macromolecules (Brooijmans and Kuntz, 2003). The docking process provides the best binding orientation between a small molecule and a potential target protein. Therefore, three-dimensional structures of macromolecules are prerequisite essential information for the docking simulation. An example of a successful application of this approach is tacrine, which inhibits acetylcholinesterase and thereby increases synaptic acetylcholine levels to enhance cognitive function in AD (Harel et al., 1993). Other examples include zanamivir, a neuroaminidase inhibitor that that interacts with the influenza virus (Xu et al., 2008); various human immunodeficiency virus protease inhibitors such as saquinavir, ritonavir, and indinavir (Andrews et al., 2006); and the COX-2 inhibitor celecoxib, which is used to treat the chronic inflammatory disorder arthritis (Price and Jorgensen, 2001).

The docking simulation generates a numerical score that is used to rank predicted ligand conformations in hit identification and lead optimization (Kitchen et al., 2004). The docking simulation will not succeed if the scores do not differentiate a correct ligand from incorrect ligands. Scoring applied to docking simulation can give an accurate estimate of the binding free energy between small molecules and macromolecules, although the score does not fully account for all physical factors that ultimately determine molecular recognition. Free-energy simulation techniques have been developed for the prediction of binding affinity between small molecules and a macromolecular target (Simonson et al., 2002). The information on binding between target molecules and compounds, such as those dominated by shape complementarity, can be used to establish approximations of positioning and scoring. In addition, it is also a common practice to include more subjective visual inspection, which adds another dimension to the selection process (Doman et al., 2002).

Several studies have used computational docking simulations to screen phytochemical libraries. For example, 25,000 phytochemicals were evaluated to identify potential inhibitors of ER-β (Zhao and Brinton, 2005). In another study, the phytochemical ellagic acid was identified as an inhibitor to casein kinase 2, which is involved in prostate cancer (Cozza et al., 2006). Plant-derived SdiA-selective ligands were found to be antibacterial agents with potential for treatment of urinary infections (Ravichandiran et al., 2012). Collections of large numbers of phytochemicals for high-throughput screening are available in academic and government laboratories as well as in pharmaceutical companies. The following databases of phytochemicals are available: PubChem (pubchem.ncbi.nlm.nih.gov), ZINC (zinc.docking.org), Asinex (www.asinex.com), and Dictionary of Natural Products (dnp.chemnetbase.com). Such databases include structural information on many phytochemicals. The ligand databases increase the probability of identifying high-potency ligands.

We performed a docking simulation to evaluate the reliability of phytochemical screening against target macromolecules known to be affected by certain phytochemicals, including Nrf2, mTOR, and GSK-3β. Nrf2, a master redox switch that induces expression of cytoprotective genes, is activated by curcumin, EGCG, lycopene, sulforaphane, and resveratrol (Surh et al., 2008). For docking simulation, we used the crystal structure of Nrf2 taken from the Protein Data Bank archives (2FLU). Using the Dock6 program, we calculated the docking score between Nrf2 and three phytochemicals (curcumin, EGCG, and sulforaphane). The program predicted that all three phytochemicals bound to Nrf2 with high binding scores as follows: curcumin, −45.37 kcal/mol; EGCG, −37.16 kcal/mol; and sulforaphane, −31.42 kcal/mol (Fig. 8). Interestingly, the three phytochemicals were bound to different pockets of Nrf2. The results could suggest that each phytochemical has a different molecular site of action to activate Nrf2, which provides insight for future studies of the potential effects of phytochemical cocktails on Nrf2. In addition, we tested the docking simulation between mTOR and two phytochemicals (rapamycin and fisetin). Rapamycin had a higher binding score (−96.51 kcal/mol) compared with fisetin (−31.54 kcal/mol) (Fig. 9). The high binding score of rapamycin is consistent with its known inhibitory effect on mTOR. Therefore, the docking simulation provides the opportunity to find other candidates from phytochemical databases that have scores approaching that of rapamycin. We also calculated the docking score

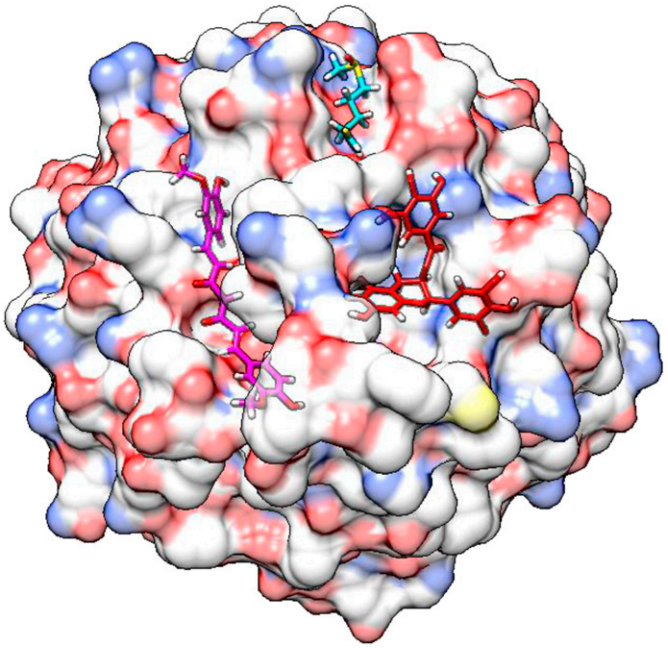

Fig. 8. Docking simulation between Nrf2 and three phytochemicals. The crystal structure of Nrf2 was taken from the Protein Data Bank archives (ID: 2FLU). For docking simulation, the Dock6 program and the tool's manual were used. Docking scores were calculated for the interactions of the receptor and three phytochemicals (sulforaphane, curcumin, and EGCG). The binding score of curcumin (magenta) was −45.37 kcal/mol. The binding scores for sulforaphane (cyan) and EGCG (red) were −31.42 kcal/mol and −37.16 kcal/mol, respectively.

of GSK-3β with two phytochemicals (kenpaullone and morin). Kenpaullone is a paullone that is known to be a selective inhibitor of GSK-3β with an IC_{50} value in the nanomolar range (Leost et al., 2000; Bain et al., 2003; Meijer et al., 2004). It was reported that the flavonol morin effectively inhibits GSK-3β activity and blocks GSK-3β–induced τ phosphorylation (Gong et al., 2011). A docking simulation model based on the computational approaches revealed that both phytochemicals have high potential complementarity to bind into the structures of GSK-3β within the ATP-binding pocket (Fig. 10). The results suggest that the ATP-binding pocket is an important site of binding for phytochemicals that inhibit GSK-3β activity (Leost et al., 2000).

B. Pharmacophore-Based Screening. In ligand-based drug screening, the most effective lead compounds are detected using a pharmacophore search (Reddy et al., 2007). Pharmacophore is the ensemble of steric and electronic features of ligands for interacting with macromolecules. The pharmacophore-based screening approach finds effective lead compounds from large compound databases using several features of active compounds such as hydrogen bond acceptor and donor, positive and negative ionizable area, hydrophobic area, and aromatic ring structure (Fig. 11). The pharmacophore information is used to index functional groups or molecular fragments within their structures (Harvey et al., 2010). Traditionally, pharmacophore-based approaches have been used in drug discovery. However, many drug candidates developed by the pharmacophore approach failed in clinical trials. For this reason, recent

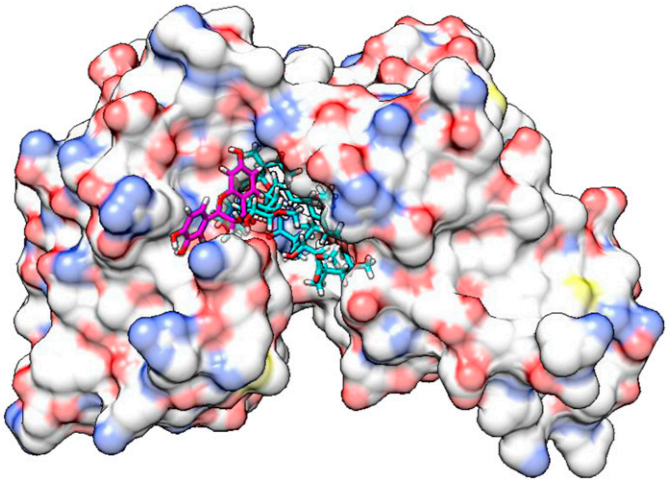

Fig. 9. Docking simulation between mTOR and two phytochemicals. The crystal structure of the mTOR was taken from the Protein Data Bank archives (ID: 1NSG). We calculated the docking score between the receptor and two ligands (rapamycin and fisetin). The binding affinities were −96.51 kcal/mol for mTOR with rapamycin (cyan) and −31.54 kcal/mol for fisetin (magenta).

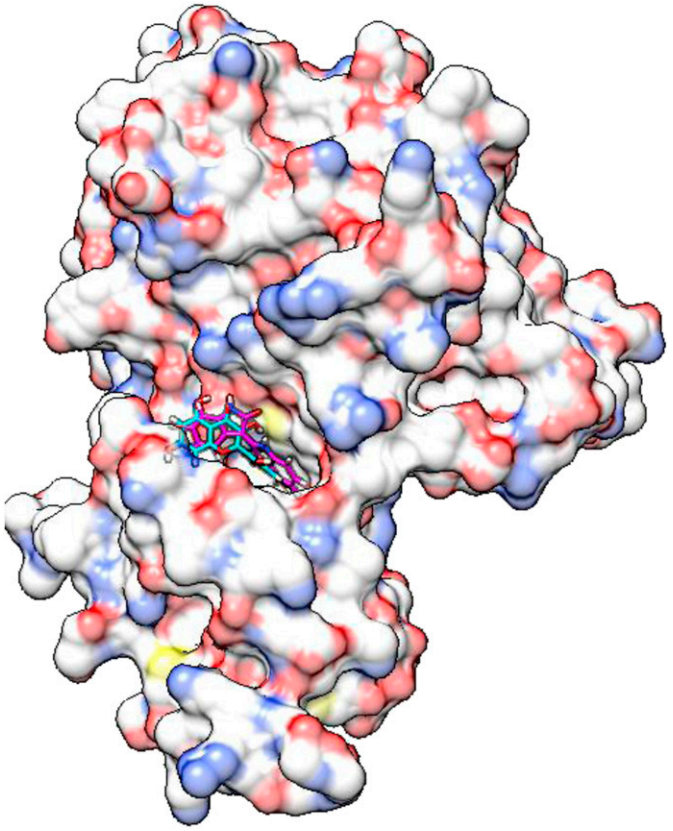

Fig. 10. Docking simulation between GSK-3β and two phytochemicals. The crystal structure of the GSK-3β was taken from the Protein Data Bank archives (ID: 1I09). The docking scores for the interaction of the target protein and two ligands kenpaullone (magenta) and morin (cyan) were 35.20 kcal/mol and −32.73 kcal/mol, respectively.

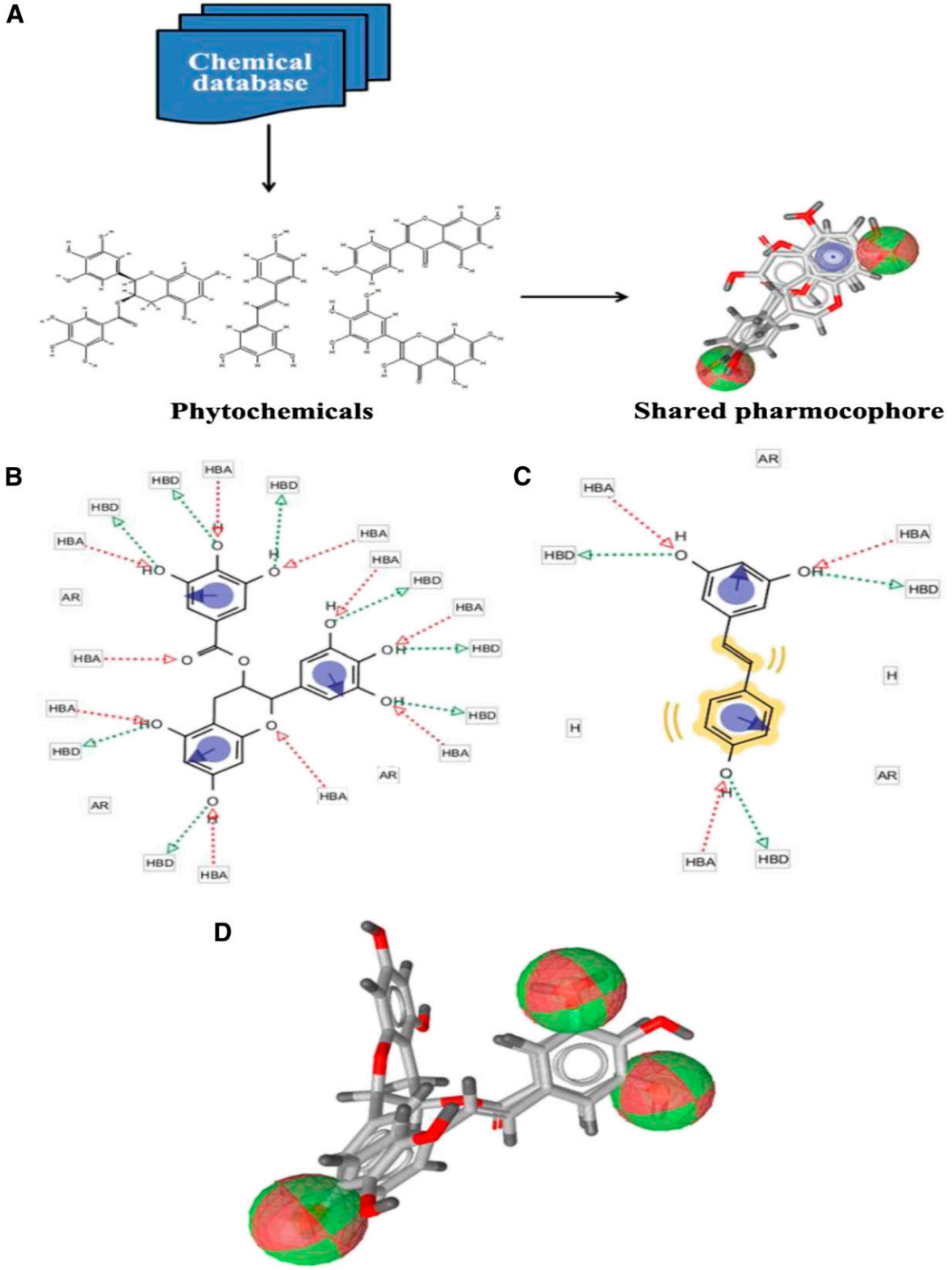

Fig. 11. Approaches for identifying phytochemicals that interact with specific protein targets involved in adaptive cellular stress responses. (A) Schema of the pharmacophore prediction approach. (B) Identification of the common pharmacophore for EGCG (left) and resveratrol (right). Red lines and circles show the hydrogen bond acceptor and the green lines and circles denote hydrogen bond donors. The two compounds share three pharmacophore sites (hydrogen bond acceptor and hydrogen bond donor). (C) The pharmacophore model was generated using the LigandScout 3.0 program. AR, aromatic ring; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor.

strategies focus on integrative profiling including the following: pharmacophore mapping; absorption, distribution, metabolism, and elimination toxicity profiling; and docking simulation of new molecules to select optimal drug-like compounds for large molecular libraries (Winiwarter and Hilgendorf, 2008; Wang and Skolnik, 2009). Furthermore, the docking results between the ligand and target macromolecule can be verified using a pharmacophore model (Pedretti et al., 2011).

Recent pharmacophore-based screenings of phytochemical libraries have been reported. Rollinger et al. (2004) used a structure-based pharmacophore model to correctly retrieve active acetylcholinesterase inhibitors from 11,000 natural products. Zhao and Brinton (2005) carried out screening of a natural source chemical collection containing 25,000 phytochemicals and derivatives, and 12 representative hits were assessed for their binding profiles to ERs, a drug target for breast cancer; three phytochemicals displayed >100-fold binding selectivity to ERβ compared with ERα. Li et al. (2013c) reported the screening of nine flavonoids from the ZINC and PubChem databases (which include 2092 flavonoids) against the xanthine oxidase and COX-2 three-dimensional protein structures using docking simulation and structure–activity relationships. In addition, Tanrikulu et al. (2009) used pharmacophore models to find potential PPARγ agonists from approximately 53,000 compounds found in plants used in traditional Chinese medicine. Finally, Wolber and Langer (2005) performed a pharmacophore-based analysis to determine the reliability of ligand-based drug screening from phytochemicals using the LigandScout 3.0 program. The latter study showed that EGCG and resveratrol share three pharmacophore features. The pharmacophore analysis can therefore provide a framework to study ligand–receptor interactions that should assist in the discovery of phytochemicals that modify adaptive cellular stress response pathways, and to then rationally design analogs of those phytochemicals for drug development.

VII. Conclusions and Future Directions

The realization that many of the major phytochemicals initially touted as exerting health benefits by acting as free radical scavengers instead act by inducing adaptive cellular stress responses is leading to new approaches to disease prevention and treatment. Evolutionary considerations and experimental evidence have established that plants produce chemicals that are noxious for insects and other pests as a fundamental defense mechanism. In turn, insects and higher organisms have evolved receptors and signal transduction pathways that respond to the phytochemicals in ways that alert the organism to the presence of the potentially toxic phytochemicals (e.g., olfactory and taste receptors) and upregulate the expression of genes encoding cytoprotective proteins. Moreover, animals have evolved enzymes (principally P450s) that rapidly metabolize and detoxify the phytochemicals. In this way, the chemicals cause only a transient activation of adaptive stress response pathways in cells. The adaptive stress response pathways are highly conserved from invertebrates to humans and include those involving transcription factors such as Nrf2, NF-κB, FOXO, and PPARs. Targets genes induced by hormetic phytochemicals include antioxidant enzymes, protein chaperones, and neurotrophic factors. Activation of these pathways in neurons can increase their resistance to oxidative, metabolic, and excitotoxic injury, resulting in reduced damage and death of neurons in experimental models of disorders ranging from AD and PD to stroke.

What is next? There is a considerable gap in our understanding of the specific molecular mechanisms by which phytochemicals stimulate adaptive cellular responses. In some cases, it is clear that a phytochemical can activate a cell surface receptor in a highly specific manner, with activation of the transient receptor potential vanilloid receptor 1 by capsaicin (from hot peppers) and cannabinoid receptors by Δ^9-tetrahydrocannabinol (from *Cannabis sativa*) being prominent examples (Croxford, 2003; Brederson et al., 2013). However, in most cases in which phytochemicals have been shown to activate adaptive cellular stress response pathways, the molecular mechanism by which they activate the pathway is unknown. Whereas some phytochemicals may bind and activate specific receptors, others may elicit a less specific response by inducing oxidative or metabolic stress. From an evolutionary perspective, dose-dependent nonspecific cellular stress responses to a phytochemical may have been sufficient to limit amount of the plant consumed by the forager, while at the same time bolstering cellular defenses.

A second largely untouched area of phytochemical-mediated hormesis is to identify the specific phytochemicals in vegetables, fruits, nuts, and grains that may improve health and disease resistance by stimulating adaptive stress responses. There has been much focus on a small number of phytochemicals (particularly resveratrol, curcumin, and sulforaphane) that likely represent only the tip of the iceberg of bioactive dietary phytochemicals. The current approaches in natural products chemistry are rather laborious, and there is thus a need to develop new approaches and technologies for identifying beneficial phytochemicals. One such approach is to develop high-throughput screens to identify phytochemicals that activate specific adaptive cellular stress response pathways.

With regard to phytochemical-based drug development, it will be important to not only perform the typical pharmacokinetic, safety, and target engagement analyses, but to also include intermittent dosing protocols into preclinical studies and clinical trials.

Emerging evidence suggests that intermittent (e.g., every other day) exposure to mild stressors can promote optimal health and may be effective in forestalling and treating a range of disorders. For example, intermittent fasting and exercise can improve overall health and reduce the risk of a range of chronic age-related disorders (Mattson, 2012; Longo and Mattson, 2014). The data suggest that cycles of mild stress followed by a recovery period are superior to continual stress or no stress. It will therefore be important to determine whether intermittent dosing with phytochemicals provides health benefits beyond any that occur with continuous dosing. When considering the therapeutic efficacy of drugs that act by bolstering cellular defenses against injury and disease, we would expect that drugs administered intermittently will be more effective than those dosed so as to achieve a constant tissue level of the drug. This is so because cycles of stress (e.g., recovery, stress, and then recovery) stimulate adaptive stress response pathways during the stress period, and then allow the cells/organism to grow stronger during the recovery period. In this way, intermittent activation of adaptive stress response pathways by phytochemicals can enhance cellular resistance to injury and disease.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Lee, Jo, Park, Chung, Mattson.

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