Flavonoid-Based Therapies in the Early Management of Neurodegenerative Diseases[1,2]

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ABSTRACT

During the past several years, there has been enormous progress in the understanding of the causative factors that initiate neuronal damage in various neurodegenerative diseases, including Alzheimer disease, Parkinson disease, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington disease. Preventing neuronal damage and neuronal death will have a huge clinical benefit. However, despite major advances in causative factors that trigger these neurodegenerative diseases, to date there have been no therapies available that benefit patients who suffer from these diseases. Because most neurodegenerative diseases are late-onset and remain asymptomatic for most of the phases, the therapies initiated in advanced stages of the disease have limited value to patients. It may be possible to prevent or halt the disease progression to a great extent if therapies start at the initial stage of the disease. Such therapies may restore neuronal function by reducing or even eliminating the primary stressor. Flavonoids are key compounds for the development of a new generation of therapeutic agents that are clinically effective in treating neurodegenerative diseases. Regular consumption of flavonoids has been associated with a reduced risk of neurodegenerative diseases. In addition to their antioxidant properties, these polyphenolic compounds exhibit neuroprotective properties by their interaction with cellular signaling pathways followed by transcription and translation that mediate cell function under both normal and pathologic conditions. This review focuses on human intervention studies as well as animal studies on the role of various flavonoids in the prevention of neurodegenerative diseases. *Adv Nutr* 2015;6:64–72.

Keywords: flavonoids, bioactive compounds, neurodegenerative diseases, neuroprotection, mitochondria, oxidative stress, antioxidant, cellular signaling, cognitive functions

Introduction

Neurodegeneration is the slow and progressive loss of neuronal cells in specified regions of the brain and is the main pathologic feature of various neurodegenerative diseases such as Alzheimer disease (AD)[3], Parkinson disease (PD), multiple sclerosis (MS), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS) (1, 2). The main causes of neurodegeneration in these diseases, along with normal brain aging, are several cellular and molecular events such as oxidative stress, impaired mitochondrial function, deposition of aggregated proteins, neuroinflammation, and activation of apoptotic factors (2). Despite enormous progress in understanding the pathogenesis of neurodegenerative diseases, the treatment of most of those conditions are still obscure. Because, in most cases, neurodegenerative diseases begin very early in life and symptoms appear very late, early diagnosis and appropriate therapeutic intervention are necessary to stop the progression of disease and suffering of patients. Flavonoids are bioactive components that are derived from fruit and vegetables. Since ancient times, flavonoid- and nonflavonoid-rich nutraceuticals have been used as food supplements in improving cognitive function and in prevention of neurodegenerative diseases in humans (3). Flavonoid-enriched extracts should be given strong consideration as novel therapies to prevent neurodegenerative diseases because of their potential beneficial effects on human health. These flavonoids may be able to target multiple sites in the brain and prevent neurodegenerative diseases. In this review, we emphasize the protective and preventive functions

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[3] Abbreviations used: Aβ, amyloid β; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; AP-1, activated protein 1; ASK1, apoptosis signal-regulating kinase-1; *Bad*, *BclxL/Bcl2*-associated death promoter; *Bax*, BCL2-associated X protein; BBB, blood-brain barrier; *Bcl2*, B-cell CLL/lymphoma 2; *Bclw*, BCL2-like 2; Bcl-xL, BCL2-like 1; BDNF, brain-derived neurotrophic factor; CREBP, cAMP response element binding protein; EGCG, epigallocatechin gallate; ERK, extracellular signal-regulated protein kinase; HD, Huntington disease; HO-1, heme oxygenase-1; iNOS, inducible NO synthase; JNK, c-Jun N-terminal kinase; *Mdm2*, murine double minute 2; MPTP, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; Nrf2, NF-E2–related factor 2; PD, Parkinson disease; PI3K/Akt, phosphatidylinositol-3 kinase/Akt; PKC, protein kinase C; SOD, superoxide dismutase; 6-OHDA, 6-hydroxydopamine.
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of flavonoids in neurodegenerative diseases by modulation of neurosignaling pathways.

Flavonoids: Their Classification, Sources, and Brain Penetration

Flavonoids are a group of diverse, low-molecular-weight plant polyphenolic compounds. They possess unique biological properties that may be responsible for many health benefits. Flavonoids are natural products widely distributed in the plant kingdom, and >6000 types of flavonoids currently have been identified. Flavonoids may be divided into 6 subclasses on the basis of their structural variations. These subclasses include the following: *1*) flavonols, *2*) flavanols, *3*) isoflavones, *4*) anthocyanidins, *5*) flavanones, and *6*) flavones (4). The subclasses, their representative flavonoids, and their common food sources are described in **Table 1**.

To understand whether flavonoids and their metabolic derivatives are capable of direct neuroprotective action, it is critical to establish if they are able to access the central nervous system. However, there is little information available on their ability to cross the blood-brain barrier (BBB) to access the central nervous system. In a model of brain endothelial cells, several flavonoids and their conjugated metabolites were found to penetrate the BBB (5). In particular, hesperetin and naringenin, and their in vivo metabolites, along with cyanidin-3-rutinoside and pelargonidin-3-glucoside were shown to cross the BBB (6). In most experiments, flavonoids are directed into the brain either by intravenous or by oral administration. Naringenin, when administered by intravenous route, was shown to enter the brain of animals (7). Similarly, epicatechin (8), anthocyanins (9), and epigallocatechin gallate (EGCG) (10) through oral administration were also found to enter the brain. Thus, these results show that flavonoids are able to cross the BBB and localize in the brain, suggesting that they are important candidates for direct neuroprotective and neuromodulatory actions.

TABLE 1 Main groups of flavonoids, their representative flavonoids, and common sources

Groups	Flavonoids	Common sources
Flavonols	Rutin Quercetin Kaempherol Myricetin	Leeks, onions, broccoli, kale, apples, cherries, berries, tea, red wine
Flavanols	Catechin Epicatechin Epigallocatechin EGCG[1]	Green tea, red wine, chocolate, apples
Isoflavones	Genistein Daidzein Glycetin Formanantine	Legumes, soybeans, soy products
Anthocyanidins	Cyanidin Malvidin Pelargonidin Delphinidin	Red wine, berry fruits, cherries, grapes
Flavanones	Hesperetin Naringenin Isoxanthohumol Taxifolin	Citrus fruits, tomatoes
Flavones	Apigenin Luteolin	Parsley, celery

[1] EGCG, epigallocatechin gallate.

Flavonoids: treatments in neurodegenerative diseases

Neurodegenerative diseases are characterized by different structural and pathologic conditions; thus, a variety of targets and more efficient methods are required for their treatment. Flavonoids exert beneficial effects on the body by affecting multiple cell systems. Flavonoids can modulate the activity of various metabolic pathways to reduce cognitive decline and neuronal dysfunction (11) and are thought to delay or even prevent the onset of neurodegenerative diseases at their effective doses or concentrations (**Table 2**). Here, we discuss the role of various flavonoids and their specific doses in the prevention or treatment of various neurodegenerative diseases.

AD. AD is a late-onset, progressive, age-dependent neurodegenerative disease that is mainly characterized by decline in memory, impairment of cognitive function, and irreversible loss of neurons, mainly in the cortex and hippocampus regions of brain (12). Neuropathologically, AD is measured by the presence of amyloid plaques, neuritic plaques, and neurofibrillary tangles. These plaques are mainly formed because of accumulation of amyloid β (Aβ) and abnormal concentrations of tau protein; thus, both of these proteins can be considered to be important biomarkers in the pathology of AD (13).

Recently, naturally occurring flavonoids were marked as potential candidates for the prevention and treatment of AD. As discussed earlier, AD is characterized by the presence of amyloid plaques, neuritic plaques, and neurofibrillary tangles, which are mainly formed due to accumulation of Aβ and abnormal tau concentrations. Thus, flavonoids that inhibit the formation of these plaque-forming factors can be used for the prevention of AD. Myricetin (0.1–1 μM) (14), rutin (0.1–1 μM) (15), and fisetin (25 mg/kg) (16) inhibited the formation and aggregation of Aβ fibrils at their effective concentrations. Cognitive function and learning ability in rats were found to be improved by long-term administration of EGCG and a preparation of green tea catechins (17). Green tea flavonoids can also protect against Aβ-induced cytotoxicity in primary rat cortical neurons (18). The neurotoxicity of Aβ is also increased by the presence of acetylcholinesterase. Thus, flavonoids present in green and white tea extracts can be used as acetylcholinesterase inhibitors in the treatment of AD (19). The neuroprotective potential of flavonoids in AD is shown not only in Aβ-induced neuronal death models but also in oxidative stress–induced neuronal death. Studies showed that flavonoids present in Ginkgo biloba extract (10–100 μg/mL) were able to protect hippocampal cells against Aβ peptides or oxidative stress–induced toxicities (20). Moreover, the neuroprotective effects of flavonoids such as EGCG (21) and genistein (40 μM) (22) were shown to be effective via scavenging of reactive oxygen species induced by Aβ. In addition, Aβ-mediated increases in reactive oxygen species production can be substantially lowered by preincubation of neuronal cells with 50 μM kaempferol

TABLE 2 Various flavonoids and their specific doses or concentrations in the prevention or protection of neuronal cells against neurodegenerative diseases

Neurodegenerative diseases	Flavonoids	Doses	Reference
Alzheimer disease	Myricetin	0.1–1 μM	(14)
	Morin	0.1–1 μM; 1 μM, 10 μM	(14, 29)
	Rutin	0.1–1 μM	(15)
	Quercetin	0.1–1 μM	(15)
	Fisetin	25 mg/kg	(16)
	Ginkgo biloba extract	10–100 μg/mL	(20)
	Genistein	40 μM	(22)
	Kaempferol	50 μM	(23)
	Apigenin	50 μM	(23)
	Anthocyanin	100 μM	(24)
	Glycitein	100 μg/mL	(26)
Parkinson disease	Quercetin	50, 100, and 200 mg/kg body weight	(37)
	Green tea catechin	0.5 and 1 mg/kg	(40)
	Acacetin	10 mg/kg per day	(41)
	Rutin	25 mg/kg body weight	(43)
	EGCG[1]	2 and 10 mg/kg; 200 μM, 5 mg/kg	(40, 42)
	Genistein	10 mg/kg	(44)
	Tangeretin	10 and 20 mg/kg	(48)
Huntington disease	EGCG	~1 μM; 10, 20 and 40 mg/kg	(54, 58)
	Naringin	80 mg/kg body weight	(55)
	Quercetin	25 mg/kg body weight	(57)
	Eriodictyol	100 μM	(59)
Amyotrophic lateral sclerosis	EGCG	>2.9 μg/g body weight; 10 mg/kg	(61, 62)
	Genistein	16 mg/kg	(63)
Multiple sclerosis	EGCG	10 μg/mL	(67)
	Luteolin	20–80 μM	(68)
	Quercetin	20–80 μM	(68)
	Fisetin	20–80 μM	(68)

[1] EGCG, epigallocatechin gallate.

and apigenin (23) and 100 μM anthocyanin in neuro-2a (N2a) neuroblastoma cells (24). Furthermore, oxidative stress was found to be lowered by rutin in SH-SY5Y neuroblastoma cells along with a reduction in malondialdehyde and glutathione disulfide formation (25). However, Aβ toxicity can also be reduced by the inhibition of Aβ deposition via the antioxidative activity of the soy isoflavone glycitein (100 μg/mL) (26). Apigenin ameliorates AD-associated learning and memory impairment via inhibiting Aβ deposition and decreasing insoluble Aβ concentrations, inhibiting oxidative stress, and improving the antioxidative enzyme activity of superoxide dismutase (SOD) and glutathione peroxidase (27). Another major plaque-forming factor in AD, abnormal concentrations of tau protein, have been shown to be neutralized by grape flavonoids (28). In addition, morin (1 and 10 μM) was also found to prevent neuronal apoptosis against tau hyperphosphorylation (29). In addition to flavonoids, nonflavonoid polyphenols also show neuroprotective effects in various neurodegenerative diseases including AD. Resveratrol extracted from grapes was found to reduce hippocampal neurodegeneration and learning impairment in an inducible p25 transgenic mouse model of AD (30). Curcumin, a nonflavonoid polyphenol found abundantly in *Curcuma longa* (turmeric), plays a beneficial role in patients with AD and in animal models of neurodegenerative disease. Curcumin was found to protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from Aβ-induced toxicity through its antioxidant activity (31). Phenolic acids constitute another family of nutraceuticals that protect the brain. These include rosmarinic and carnosic acid, which are found in rosemary and are also effective in protecting neuronal function. Rosmarinic acid was shown to protect memory impairment associated with Aβ neurotoxicity in mouse models of AD (32). Carnosic acid was also found to protect the hippocampus against Aβ-induced neurodegeneration in AD (33). Nonflavonoid organosulfur nutraceuticals, such as allicin (abundantly present in garlic), also play neuroprotective roles in a variety of neurodegenerative disease models. Garlic extract was found to protect against Aβ-induced neurocytotoxicity and inhibits caspase-3 activity, the executioner protease of the apoptotic cascade (34). These studies showed that flavonoids and other natural compounds have the ability to reduce oxidative stress and Aβ and tau toxicity and to inhibit apoptosis, thus showing therapeutic potential for prevention of or treatment for AD.

PD. PD is the second most common progressive neurodegenerative disease and is characterized by slowness of movement (bradykinesia), resting tremors, rigidity, and postural instability. Along with these symptoms, individuals with PD also show autonomic, cognitive, and psychiatric disturbances. PD is caused by persistent degeneration of dopamine-producing neurons that project from the substantia nigra pars compacta region to the striatum, which controls voluntary movement (35). The pathogenesis of PD is characterized by the misfolding and aggregation of proteins (36) along with

mitochondrial dysfunction and successive oxidative stress. Thus, in PD, agents such as flavonoids that can target oxidative stress and mitochondrial dysfunction can be prime candidates for neuroprotection.

Studies showed that flavonoids such as quercetin (50, 100, and 200 mg/kg body weight) markedly improved the motor balance and coordination in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; a parkinsonism-inducing neurotoxin)–treated mice, and significant increases were observed in the activities of various antioxidants such as glutathione peroxidase, SOD, and Na-K ATPase (37). In neurons, the administration of quercetin not only attenuated microglia activation (a precursor of PD pathogenesis) but also suppressed cell death (38). Studies have demonstrated that the consumption of green and black tea had beneficial effects in reducing the risk of PD (39). In another study, green tea extract (0.5 and 1 mg/kg) or isolated EGCG (2 and 10 mg/kg) prevented striatal dopamine depletion and loss of dopaminergic neuron in the substantia nigra of mice chronically treated with MPTP (40). In a recent study, acacetin (5,7-dihydroxy-4′-methoxyflavone), a constituent of a flavone naturally present in plants, also inhibited the degeneration of dopaminergic neurons and depletion of dopamine concentrations induced by MPTP toxicity in the substantia nigra and striatum of the brain at a dose of 10 mg/kg per day (41). PD caused by 6-hydroxydopamine (6-OHDA) was also shown to be prevented by EGCG (200 μM) in PC12 cells (42) or by rutin (25 mg/kg body weight) in male Wistar rats (43). 6-OHDA–induced toxicity and rotational behavior in lesioned rats were also found to be attenuated by genistein (10 mg/kg) (44). Luteolin (6–13 μM) increased cell survival and mitochondrial ATP levels in 3-hydroxykynurenine and 6-OHDA–induced neurotoxicity in human SH-SY5Y neuroblastoma cells and improved mitochondrial function (45). In another study, 1-methyl-4-phenylpyridinium ion [(MPP)+]-induced toxicity in mixed ventral mesencephalic cultures was significantly attenuated by quercetin in PD (46). Flavonoid-rich Ginkgo biloba extract also was found to protect against dopaminergic neurons in an animal model of PD (47). Furthermore, the citrus flavonoids, such as tangeretin (10 mg/kg per day for 28 d and 20 mg/kg per day for 4 d), were observed to maintain nigrostriatal integrity against 6-OHDA–induced neurotoxicity (48). Certain nonflavonoid nutraceuticals also revealed neuroprotective potential in PD models. Resveratrol functioned as an antioxidant and protected against 6-OHDA–induced toxicity in a rat model of PD (49). In MPTP-induced neurodegeneration, curcumin is neuroprotective and was shown to prevent glutathione depletion and lipid peroxidation in the nigrostriatal tract in mice (50). Rosmarinic acid was effective in protecting SH-SY5Y human neuroblastoma cells against hydrogen peroxide–induced oxidative stress and cell death (51). Nonflavonoid organosulfur nutraceutical compounds such as L-sulforaphane, which is abundantly found in broccoli and other cruciferous vegetables, were also shown to effectively protect against dopamine quinone–induced neuronal death (52). These results suggest that flavonoid and nonflavonoid nutraceuticals may serve as potential neuroprotective agents against the underlying pathology associated with PD.

HD. HD is a genetic autosomal disease. It is clinically characterized by psychiatric disturbances, involuntary movements, progressive cognitive impairment, choreoathetosis, dementia, and premature death. Similarly, HD is pathologically characterized by selective degeneration of deep layers of the cerebral cortex and γ-aminobutyric acid–producing striatal neurons, resulting in a progressive atrophy of the caudate and putamen nucleus and globus pallidus (53). The genetic defect responsible for HD is the expansion of a cytosine adenine guanine (CAG) trinucleotide repeat in the Huntingtin gene. Because there is ongoing active research into potential therapies for the treatment or prevention of HD, some flavonoids are considered as specific therapies for HD.

Studies showed that various types of flavonoids such as EGCG (~1 μM) (54) exhibited potential for prevention or treatment of the pathogenesis of HD. In addition, naringin (80 mg/kg body weight per day) (55), hesperidin (56), and quercetin (25 mg/kg body weight) (57) administration were also found to be preventive in 3-nitropropionic acid–induced HD. In another study, EGCG (10, 20, and 40 mg/kg) significantly improved memory function and restored glutathione system functioning in 3-nitropropionic acid–induced HD (58). Flavonoids present in citrus fruit such as eriodictyol (100 μM) increased the concentrations of intracellular glutathione and thus can also be used in the prevention of HD (59). These studies suggest that flavonoids can be used as a potential therapeutic agents in the prevention and treatment of chemically induced HD. Thus, if used in effective concentrations, they could also aid in the prevention of HD during normal disease progression.

ALS. ALS is a fatal motor neuron disease characterized by the selective degeneration of the anterior horn cells of the spinal cord and cortical motor neurons, leading to muscle weakness and paralysis. Approximately 10% of cases of ALS are familial and caused by mutations in the copper-zinc SOD type 1 gene (60), although the majority of cases are sporadic. Because ALS is a multifactorial disease, bioactive compounds such as flavonoids that target more than one aspect are needed to fight this devastating disease.

With regard to the role of flavonoids in ALS, very few studies have been reported. In one study, EGCG (>2.9 μg/g body weight) was found to protect motor neurons in wild-type and G93A SOD1 mutant mice from oxidative stress–induced cytotoxicity in an ALS mouse model (61). In another study, EGCG (10 mg/kg) significantly increased the number of motor neurons, reduced microglial activation and NF-κB concentration, and reduced the concentration of inducible NO synthase (iNOS) (62). In addition, genistein (16 mg/kg) was also investigated as a prophylactic agent against ALS (63). Thus, studies show that flavonoids protect against the pathogenesis of ALS.

MS. MS is a chronic disease of the central nervous system characterized by neurodegeneration, demyelination, and

astroglial proliferation (64), affecting both white and gray matter of neuronal cells. Clinically, MS is characterized by relapsing-remitting phenotypes and neuropathologic manifestations in which the patient experiences clinical attacks causing neurologic dysfunction including optic neuritis and transverse myelitis. Neuropathologically, MS can be characterized by inflammation, demyelination, and axonal degeneration (65).

MS is a neuroinflammatory disease, and flavonoids are naturally occurring immunomodulatory compounds that can limit demyelination, reduce neuroinflammation, and downregulate immune function. Studies have shown that flavonoids such as luteolin (66) and EGCG (10 μg/mL) (67) provide neuroprotection by reducing neuroinflammation and axonal damage. In addition, flavonoids such as luteolin, quercetin, and fisetin at concentrations of 20–80 μM are able to decrease the amount of myelin phagocytosed by macrophages and thus can be preventive of MS (68). In MS, IL-1 is mainly responsible for T cell activation and TNF-α is mainly responsible for demyelination (69). Quercetin was found to control the immune response via control of IL-1 and TNF-α peripheral blood mononuclear cells isolated from patients with MS (70). The potential of flavonoids in limiting demyelination, reducing neuroinflammation, and downregulating immune function makes them prominent therapeutic agents in age-related MS.

Molecular mechanisms of neuroprotection by flavonoids

Flavonoids are known to provide neuroprotective effects by interacting with brain tissue at multiple sites. The neuroprotective action of dietary flavonoids includes their potential to protect neurons against oxidative stress and neuronal injury via their potential as antioxidants, an ability to suppress neuroinflammation, and the potential to modulate cell signaling pathways. Flavonoids are well-known antioxidants, and they may protect cell constituents against oxidative stress and therefore reduce the risk of neurodegenerative disease associated with oxidative stress. Flavonoids also protect neurons against some neurotoxic drugs whose toxicity is linked to the stimulation of oxidative stress. Various flavonoids, such as tangeretin (48), EGCG (42), genistein (44), and rutin (43), can attenuate 6-OHDA–induced neurotoxicity in PD. In addition, MPTP-induced neurotoxicity is also decreased by EGCG (40) and quercetin (37). Flavonoids interact not only through their antioxidant potential in protecting neurons but they also modulate various cell signaling pathways (3). It has become evident that flavonoids interact with critical neuronal intracellular signaling pathways and are able to exert neuroprotective actions (11). Flavonoids and their metabolites may exert modulatory actions in cells through actions at protein kinase and lipid kinase signaling pathways. Inhibitory or stimulatory actions at these signaling pathways strongly affect neuronal function by altering the phosphorylation state of target molecules and by modulating gene expression (71). Important cell survival signaling pathways include the following: phosphatidylinositol-3 kinase/Akt (PI3K/Akt), extracellular signal–regulated protein kinase (ERK), protein kinase C (PKC), and the cell death pathways p38 and c-Jun N-terminal kinase (JNK). Various flavonoids interact with these pathways and provide protection against neurodegeneration (**Figure 1**).

Flavonoids such as EGCG (72) and hesperetin (73), flavonoid-rich blueberry extract (74), and the flavonoid baicalein (75) were found to activate PI3K/Akt, ERK, and PKC pathways. The activation of pathways by these flavonoids provides beneficial effects on cell survival via upregulation of the antiapoptotic or prosurvival genes such as B-cell lymphoma 2 (*Bcl2*), BCL2-like 2 (*Bclw*), and BCL2-like 1 (*BclxL*) (72, 75); inhibition of the proapoptotic proteins (caspase 9 and caspase 3 activation); and inhibition of apoptosis signal-regulating kinase 1 (ASK1) (73) and nontranscriptional inhibition of *BclxL/Bcl2*-associated death promoter (*Bad*), BCL2-associated X protein (*Bax*), and murine double minute 2 (*Mdm2*) (72). Flavonoids also have a protective effect on cell survival through mechanisms that may involve activation of the cAMP response element-binding protein (CREBP) phosphorylation (74), increases in the amount of brain-derived neurotrophic factor

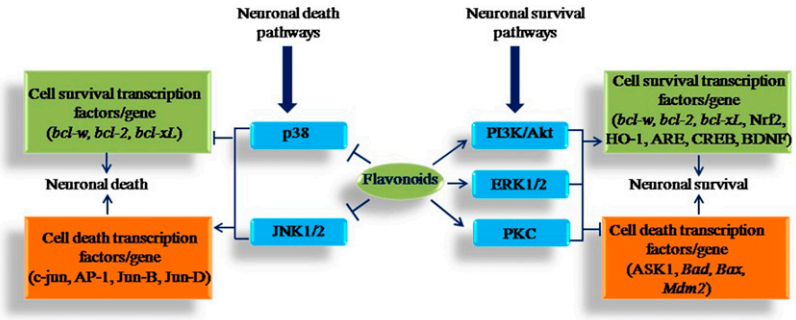

FIGURE 1 The modulation of neuronal survival and death protein kinase pathways by flavonoids. The activation of PI3K/Akt, ERK1/2, and PKC pathways acts to stimulate neuronal survival through the induction of prosurvival or antiapoptotic genes and via inhibition of proapoptotic proteins. JNK and p38 are stress-activated pathways and cause neuronal death via activation of c-Jun and other AP-1 proteins; they lead to apoptosis and neuronal death. In addition, the inhibitory actions of flavonoids within the JNK and p38 pathways are likely to be neuroprotective in the presence of stress signals. However, flavonoids have neuroprotective and neuromodulatory properties and prevent neuronal function via inhibitory and stimulatory actions at these signaling pathways. AP-1, activated protein 1; ARE, antioxidant response element; ASK1, apoptosis signal-regulating kinase 1; Bad, Bcl-xL/Bcl-2–associated death promoter; Bax, BCL2-associated X protein; bcl-w, BCL2-like 2; bcl-xL, BCL2-like 1; bcl-2, B-cell CLL/lymphoma 2; BDNF, brain-derived neurotrophic factor; CREBP, cAMP response element-binding protein; ERK, extracellular signal-regulated protein kinase; HO-1, heme-oxygenase 1; JNK, c-Jun N-terminal kinase; Mdm2, murine double minute 2; Nrf2, NF-E2–related factor 2; PI3K/Akt, phosphatidylinositol-3 kinase/Akt; PKC, protein kinase C.

(BDNF) (74), and increased transcriptional factor NF-E2–related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) protein expression and enhanced antioxidant response element transcriptional activity (75). The stimulatory effects of all of these flavonoids may be preventive against neurodegeneration and protect brain function (Figure 1).

JNK and p38 are considered to be cell death pathways because they have been strongly linked to transcription-dependent apoptotic signaling (76) via the activation of c-Jun (77) and other activated protein 1 (AP-1) proteins, including JunB and JunD. Flavonoids have antiapoptotic action via the inhibition of JNK and p38 pathways (Figure 1). Flavonoids such as quercetin (78), epicatechin and 3′-*O*-methyl-epicatechin (79), and hesperetin and its structural counterparts isorhamnetin and isosakuranetin (80) were found to inhibit JNK activity. Quercetin, hesperetin, and its structural counterparts isorhamnetin and isosakuranetin may suppress JNK activity and apoptosis induced by hydrogen peroxide (78, 80). Epicatechin and 3′-*O*-methyl-epicatechin also protect neurons against oxidative damage via a mechanism involving the suppression of JNK and its downstream partners c-Jun and pro-caspase-3 (79). There are very few studies that suggest that flavonoids modulate neuronal signaling through the p38 pathway. The p38 pathway is inhibited by genistein (81) and cocoa extract and its main flavonoid epicatechin (82). Genistein protects the neurons from Aβ-induced cell death by preventing oxidative stress, which, in turn, inhibits the activation of p38, protecting neurons from cell death (81). Epicatechin is also an important flavonoid that protects against oxidative stress–induced neurodegeneration (82). However, the above mentioned flavonoids activate or suppress various cell signaling pathways and thus show an ability to induce morphologic changes that have a direct influence on memory performance and brain function.

Neuroinflammatory processes are assumed to play a critical role in the development of various neurodegenerative diseases (83) in which glial cells play a significant role. Activated glial cells (microglia and astrocytes) lead to the production of cytokines and other inflammatory mediators that may contribute to the apoptotic cell death of neurons (84). Various flavonoids, such as those in flavonoid-rich blueberry extracts (85), luteolin (86), kaempferol (87), wogonin, bacalein (88), EGCG (89), and quercetin (90, 91), were found to inhibit production of proinflammatory mediators such as NO, TNF-α, IL-1β, and iNOS expression, cyclooxygenase-2 expression, NADPH oxidase activation, and reactive oxygen species production. All of these effects of flavonoids appear via their ability to directly modulate the cell signaling pathways (3): for example, the inhibition of cell signaling cascades, such as p38 and ERK, via flavonoids that control both iNOS and TNF-α expression in activated glial cells (92). In addition, fisetin inhibited p38 phosphorylation (93) and luteolin inhibited IL-6 production via the inhibition of the JNK pathway (94). Flavonoids were also found to prevent transcription factor activation; for example, quercetin attenuated neuroinflammation via mechanisms that involved downregulation of iNOS gene transcription by inhibition of NF-κB, which is responsible for iNOS transcription (90). Thus, all of these molecular mechanisms suggest that flavonoids might have therapeutic potential in maintaining optimal neuronal function and neurocognitive performance in various neurodegenerative diseases.

Conclusions

Dietary supplementation of flavonoids has shown several neuroprotective actions in the brain, including prevention of toxicity against various neurotoxins, decreasing neuroinflammation and oxidative stress, and the ability to enhance memory and improve cognitive function. These beneficial effects on brain function are modulated by mechanisms that involve the interaction with key neuronal signaling process leading to expression of neuronal survival and differentiation genes and the suppression of genes responsible for neurodegeneration. Thus, regular dietary supplementation of flavonoid-rich foods at an appropriate stage of neurodegeneration holds promise as a natural remedy to halt many neurodegenerative diseases and to improve cognitive and other brain functions. In view of the recent evidence on the role of flavonoids in the activation of many transcription factors and cell survival signaling pathways in the brain, it is hoped that, in the future, these compounds may represent one of a new generation of bioactive drugs for improving brain function in various neurodegenerative diseases.

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