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*Review Article*

# Natural Products for Neurodegeneration: Regulating Neurotrophic Signals

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Neurodegenerative disorders (NDs) are heterogeneous groups of ailments typically characterized by progressive damage of the nervous system. Several drugs are used to treat NDs but they have only symptomatic benefits with various side effects. Numerous researches have been performed to prove the advantages of phytochemicals for the treatment of NDs. Furthermore, phytochemicals such as polyphenols might play a pivotal role in rescue from neurodegeneration due to their various effects as anti-inflammatory, antioxidative, and antiamyloidogenic agents by controlling apoptotic factors, neurotrophic factors (NTFs), free radical scavenging system, and mitochondrial stress. On the other hand, neurotrophins (NTs) including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT4/5, and NT3 might have a crucial neuroprotective role, and their diminution triggers the development of the NDs. Polyphenols can interfere directly with intracellular signaling molecules to alter brain activity. Several natural products also improve the biosynthesis of endogenous genes encoding antiapoptotic Bcl-2 as

well as NTFs such as glial cell and brain-derived NTFs. Various epidemiological studies have demonstrated that the initiation of these genes could play an essential role in the neuroprotective function of dietary compounds. Hence, targeting NTs might represent a promising approach for the management of NDs. In this review, we focus on the natural product-mediated neurotrophic signal-modulating cascades, which are involved in the neuroprotective effects.

## 1. Introduction

Neurodegenerative disorders (NDs) are global health burdens that result from the progressive defect of neural cells, leading to dysfunction in the nervous system [1, 2]. The World Health Organization (WHO) predicts that, by 2050, people living with dementia are projected to triple from 50 million to 152 million [3]. Various NDs including Alzheimer's disease (AD), Huntington's disease, amyotrophic lateral sclerosis, Parkinson's disease (PD), and frontotemporal dementia exert a deleterious burden not only on the affected persons but also on their family members as well as the society [4, 5]. Every year, USA spends billions of dollars on uninterrupted health care expenses and lost profits, and it is assessed that $100 billion is spent only on AD each year [6]. Apart from these financial matters, there is a huge emotional and pathetic burden on AD individuals and their caretakers [7].

Several neurodegenerative diseases share similar pathogenetic mechanisms at various steps of the disease development including mitochondrial dysfunction, increased nitrosative/oxidative stress, protein aggregation/misfolding, loss of synaptic function, and reduced neuronal survival [8–11]. While immune cells and neurons are exposed to lethal proteins, higher energy is required to protect them from the deposited nitrogen and oxygen species responsible for neuronal damage. These latter induce a mitochondrial dysfunction with the release of cytochrome c along with other mitochondrial proteins thus leading to cell death [8, 10]. This protein accumulation disturbs cell signaling as well as neuronal functions which are considered as the main causes of neuronal disorders [12, 13].

Neurotrophins (NTs) or neurotrophic factors (NTFs) are a group of essential growth factors, which are required for the regulation, persistence, and renewal of certain neuronal cells in the brain [14, 15]. NTs have been recognized as neuronal survival-promoting proteins in animals and include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3, and NT-4/5 [16, 17]. By modulating synaptic plasticity, BDNF serves as a key molecule in neurodegenerative diseases [18, 19]. Furthermore, BDNF gene delivery is a potential therapy for tau pathology in Alzheimer's disease [20]. Some phytochemicals stimulate neuronal cell differentiation and upregulate NTs including BDNF and NGF [21–25]. Phytochemicals may thus have the potential to inhibit neurodegeneration by triggering NTs and by upregulating the function of several constituents of the antioxidant system, for example, catalase and superoxide dismutase (SOD) [26, 27]. Also, they may hinder the formation of several inflammatory mediators and reactive oxygen species (ROS) such as nitric oxide (NO), nuclear factor kappa B (NF-$\kappa$B), intrinsic nitric oxide synthase (iNOS), tumor necrosis factor-$\alpha$ (TNF-$\alpha$), prostaglandin (PG) E2, and interleukin (IL)-1$\beta$. NGF induces the tropomyosin receptor kinase (Trk) A signaling cascade [21–24] by preventing the protein expression pathway [28] and through the breakdown of amyloid $\beta$ (A$\beta$) peptides in the brain [29]. Among natural products, polyphenols, in particular, initiate NTs and have antiapoptotic as well as antioxidative actions in neurons. In this review, we present the natural products that can modulate the neurotrophic signals to treat NDs.

## 2. Cellular Interactions between Neurotrophic Factors and Their Receptors for Neuroprotection

NTFs control the development, progression, plasticity, and function of neurons and defend neuronal cells against apoptosis [30]. NTFs are divided into the neurotrophic cytokines (neurokines), the neurotrophin family, the glial cell line-derived neurotrophic factor (GDNF) family of ligands, and new NTF members, such as the mesencephalic astrocyte-derived neurotrophic factor (MANF), the cerebral dopamine neurotrophic factor (CDNF), the basic fibroblast growth factor (bFGF), and the ciliary neurotrophic factor (CNTF) [31]. NTs such as NGF, BDNF, NT-3, and NT-4 bind with two distinct receptors, namely, Trk receptors and p75 neurotrophin receptor (p75NTR). The initiation of Trk receptors stimulates the survival of neurons, while p75NTR induces cell apoptosis. NTs have a selective high affinity to different Trk receptors. For instance, TrkA displays a high affinity toward NGF, whereas TrkB and TrKC show a higher affinity toward BDNF and NT-3 and NT 4/5, respectively [32]. Several NTFs including BDNF, NT-3, NGF, NT 4/5, bFGF-2, and erythropoietin (EPO) prevent neurons from injury. Consequently, they are capable of restoring NDs by interacting with the Trk receptor and enhancing the growth, survival, and regulation of neurons [33]. Among NTs, NGF was the first identified growth factor and has been shown to improve the survival of neurons and outgrowth of neurite ganglia in terrestrial birds by using the tissues of mouse sarcoma [33]. NTs expedite distinct intracellular signaling pathways, such as the Ras/extracellular signal-regulated kinases (ERK), phosphatidylinositol 3-kinase (PI3K)/AKT, and phospholipase C$\gamma$ pathways, through their binding to the related receptors [34].

Furthermore, NTs activate downstream signaling targets to control cell survival and enhance synaptic as well as neurite outgrowth for maintaining cell volume or to increase rescue from neurodegeneration [35]. NTs accelerate the transcription of the Trk receptor via Brn3a, Kruppel-like factor 7, c-Jun, NeuroD, and cAMP response element-binding (CREB) protein [36]. NTs deficiency that inhibits the expression of the Trk receptor and may result in defects of the

cognitive neurons. Interestingly, spicatoside A, a steroidal saponin derived from *Liriope platyphylla* Wang et Tang, enhances the release of NTFs in primary astrocyte cells and C6 glioma to increase long-term potentiation [23, 37–39]. NTs also exhibit a weak affinity towards p75NTR due to structural resemblances with the receptors of the Trk family [40]. Importantly, p75NTR induces the cell death promoting the TNF receptor superfamily involving several factors, for instance, Fas ligand, TNF receptor-I, TNF receptor-II, OX40, CD40, and TNF [41]. Dimeric NTs interact with p75NTR monomers by the formation of a disulfide bond with a cysteine-rich intracellular repeating domain as well as causing a structural alteration of the receptor [42–44]. This alteration then triggers an enzymatic induction of an adaptor protein by c-Jun N-terminal kinase (JNK) and NF-$\kappa$B that lead to proliferation as well as survival through B cell lymphoma-2 (Bcl-2), or apoptosis via caspases [42–44].

NT binding causes the initiation of the Trk receptor, triggering oligomerization and transautophosphorylation of the tyrosine moiety in the intracellular domain. This event subsequently leads to the initiation of signaling transduction inside the cell through stimulation of the Ras/mitogen-activated protein kinase (MAPK) pathway resulting in CREB-dependent NT secretion and expression of Bcl-2, which finally enhances cell survival, development, and proliferation [45]. Apart from analyses reporting on the functions of NGF itself, analyses of NGF mimetics along with NGF inducers are currently in development. NGF can improve the cellular growth rate and differentiation and the development of neurite, which can positively enhance memory and learning in AD patients [46, 47]. Also, NT insufficiency plays a pivotal role in neuropathy [48]; thus, research on phytochemicals that can potentiate NT is essential to combat NDs [44]. In the brain, neurotrophic factors cannot pass through the blood-brain barrier (BBB), and various approaches have been used to increase their delivery [49, 50]. Furthermore, GDNF had administered into the putamen either directly or indirectly by the transplantation of GDNF-producing cells as well as by using gene therapy employing recombinant lentiviruses or adeno-associated viruses in some clinical studies with PD patients [51, 52]. As a different delivery approach, small molecules that can penetrate through the BBB have been advocated to enhance the endogenous NTF expression for clinical trials. Levodopa and dopamine agonists, glutamate antagonists, antipsychotics, and antidepressants increase the level of GDNF and BDNF in the brain [19, 53–55]. Selegiline and rasagiline elevate the level of BDNF and GDNF in the cerebrospinal fluid in cellular and animal models as well as PD patients [56–59]. Ras-PI3K-Akt survival pathway activation could play a role in rasagiline's neuroprotective effect in post-1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced parkinsonism [56]. Study also found that selegiline possesses trophic-like properties that are independent of MAO-B inhibition. Selegiline enhances NGF formation and protects neurons from excitotoxicity and ischemia in the central nervous system [57].

## 3. Neurotrophic Activity of Natural Products for Neuroprotection

Epigallocatechin gallate (EGCG), curcumin, epicatechin, quercetin, resveratrol, and citrus flavonoids (i.e., hesperetin and naringenin), all these compounds being polyphenols, can pass through the BBB and possess the function like NTF in the brain [60]. Various phytochemicals display neurotrophic functions by attaching with NTF receptors leading to initiation of the downstream signaling cascades as well as increased production of endogenous NTFs and receptors [9] (Figure 1).

Diosmetin (5,7,3′-trihydroxy-4′-methoxy flavone), 7,8,3′-trihydroxyflavone (7,8,3′-THF), 7,8-dihydroxyflavone (7,8-DHF), and deoxygedunin are polyphenols which form complexes by binding to TrkB, initiating PI3K-Akt-ERK cascade, enhancing BDNF, and facilitating survival of spinal ganglion neurons, hippocampal neurons, and cultivated motor neurons [61, 62]. Curcumin triggers TrkB-MAP kinase along with PI3K pathways, elevates the BDNF level, and prevents cerebral cortical neurons from glutamate excitotoxicity in rats [63]. A naturally occurring compound, 6-methylsufinylhexyl isothiocyanate (6-HITC, an analogue of sulforaphane), extracted from *Wasabia japonica* (Miq.), intensely improved the neurite outgrowth and the expression of light neurofilament-L and TrkA phosphorylation in the presence of NGF because 6-HITC that inhibits the activity of protein tyrosine phosphatase 1B, a specific phosphatase that affects the phosphorylation status of TrkA [64]. Gambogic amide, a natural compound used in Chinese medicine, also triggers the TrkA and neuroprotective signaling pathways [65]. In contrast, epicatechin was proven to prevent the expression of p75NTFR and inhibit retinal neurodegeneration in diabetic rats [66].

Furthermore, apigenin inhibits p38 MAPK, ERK1/2, and JNK as well as controls NGF-mediated neurite outgrowth in PC12 cells [67]. Apigenin has also an obvious permeability coefficient in the BBB, and therefore, it considers as a promising phytochemical for treating NDs [68]. Berberine treatment inhibits the generation of A$\beta$-induced monocyte chemotactic protein-1 and IL-6 and downregulated the expression of iNOS and Cox-2 in primary microglia as well as BV2 cells. This antineuroinflammatory effect was accomplished probably through suppression of the NF-$\kappa$B activation [69]. Curcumin weakens A$\beta$ mediated apoptosis by suppressing the activation of NF-$\kappa$B (Figure 1) stimulated by the p75NTR cell death receptor [70]. According to the study by Yang et al. [71], curcumin demonstrated a significant neuroprotective action by upregulating the expressions of BDNF TrkB and PI3K protein level via the activation of the BDNF/TrkB dependent pathway in the 6-hydroxydopamine-mediated PD rat model.

Phytochemicals stimulate other receptors for the regulation of brain functions. In animal experiments, flavonoids along with other phytochemicals have shown anxiolytic activities via the binding with receptors called $\gamma$-aminobutyric acid A (GABA-A) at the sites of nonbenzodiazepines and benzodiazepines [72–75]. Furthermore, GABA receptors

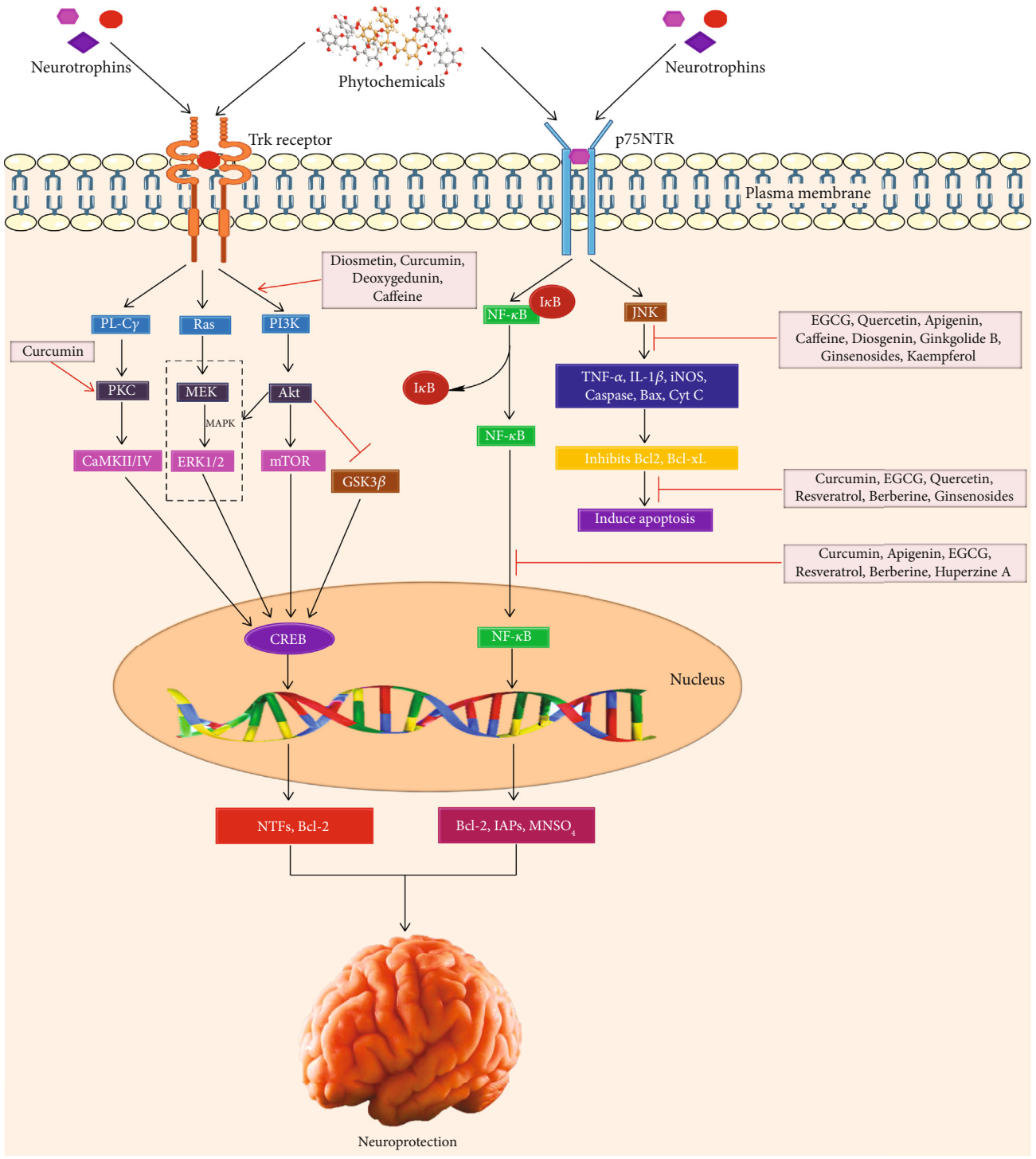


Figure 1: Role of phytochemicals involved in neuroprotection against neurodegeneration. Phytochemicals or neurotrophins bind to Trk receptor that subsequently activates PL-C$\gamma$, Ras/MAPK, and PI3K/AKT pathways. Then, these signaling cascades trigger CREB that ultimately plays a pivotal role in protecting neurons to combat neurodegeneration. Furthermore, phytochemicals or neurotrophins also attach with NGF-p75NTR receptor and activate bidirectional cell survival and apoptosis through NF-$\kappa$B and JNK signaling pathways.

induce anthocyanin-mediated neuroprotection from ethanol toxicity in prenatal rat hippocampal neurons [76] and by baicalin from global reoxygenation injury in gerbil neurons [77]. The $\alpha$4 and $\alpha$7 subunits of nicotinic acetylcholine receptors are linked with the neuroprotection afforded by scutellarin from A$\beta_{1\text{-}42}$-induced cytotoxicity in rats [78] and by EGCG in cultivated cortical neurons [79]. Curcumin prompts serotonin-1A (5-HT1A) receptor and stimulates hippocampal neurogenesis as well as the expression of BDNF in stressed rats [80] and neuroprotection against neural cell

death induced by corticosterone [81]. In depressed mouse model analyses, ethanol extracts of *Hemerocallis citrina* var. vespertina initiate ERK as well as G protein-linked receptors and subsequent cascades and exhibit antidepressant action [82] by binding to 5-HT2, 5-HT1A, and dopaminergic D2 receptors as well as noradrenergic $\alpha$1-, $\alpha$2-, and $\beta$-adrenoreceptors. The ethanol extract of *Scutellaria baicalensis* Georgi. protects cell cultures of primary rat cortical neurons against glutamate toxicity by binding with the glycine-binding site of the N-methyl-D-aspartate receptor [83]. Estrogen and insulin-like growth factor-1 (IGF-1) receptors facilitate NTF stimulation and neuronal protection by various flavonoids (i.e., calycosin, luteolin, ginsenoside Rg1, genistein) in the PD rat model [84, 85].

## 4. Signal Regulating Potential of Natural Products Involved in the Neurotrophic Function

Most of the phytochemicals directly trigger enzymes and cellular signal molecules involved in neuroprotection (Figure 1) [86, 87]. Genistein, resveratrol, EGCG, and curcumin protect neuronal cell cytotoxicity towards A$\beta$ and 6-hydroxydopamine (6-OHDA) by the initiation of the cytoprotective protein kinase C (PKC) [88–91]. Phytochemicals activate tyrosine kinase, MAPK, PKC, PI3K/Akt, Ras-MEK1/2-ERK1/2 signalling pathway, and phosphorylate CREB, which play essential roles in enhancing the expression of target genes by binding with the CREB-binding protein (CBP) [92]. PKC-ERK1/2 signaling inhibits the decline of Bcl-2, Bcl-xL, and Bcl-w and raises the cytotoxic caspases (caspase-1, -7, -10), Bax, and Bad. Caffeine triggers the PI3K/Akt signaling cascade and inhibits cell death in in vitro cellular PD models through upregulation of the antiapoptotic Bcl-2 function [93]. Besides, ferulic acid deactivates Bad by reducing the downregulation of MEK-ERK-90 kDa ribosomal S6 kinase signaling in ischemia rats [94]. Flavonoids initiate Akt-ERK1/2 signaling and prevent proapoptosis of Bim and Bad and initiation of caspases (i.e., caspase-3, caspase-9) to defend neural cells against death [95].

Carotenoids (i.e., lutein, astaxanthin, and lycopene) stimulate nuclear factor erythroid-derived 2-related factor 2 (Nrf2) (Figure 2) by binding with the antioxidant response element (ARE) and activate phase II enzymes including glutathione S-transferases (GSTs), glutathione reductase (GR), NAD(P)H quinone oxidoreductase, glutathione peroxidase (GPx), and SOD [96]. Akt induces phosphorylation of forkhead box O3 and activates NF-$\kappa$B that positively upregulates the expression of the Bcl-2 family and caspase (-3, -6, -9) inhibitors and inhibits the p53 gene [97].

Resveratrol and the citrus flavanones hesperetin and naringenin competitively block adenosine triphosphate (ATP) binding of various protein kinases via linking to the ATP-binding sites of the $Ca^{2+}$ membrane ATPase, mitochondrial ATPase, PKC, and PKA [98]. Baicalein [99], carnosol, carnosic acid [100], and hydroxytyrosol (i.e., a polyphenol from olive oil) [101] induce upregulation of endogenous antioxidant systems by dissociating the negative regulator, Kelch-like ECH association protein 1(Keap-1), from Nrf2 to stimulate the Nrf2-ARE signaling cascade. Moreover, initiation of polyphenol-mediated Nrf2-ARE signaling exerts neuroprotective effect by inducing heme oxygenase-1 (HO-1) expression in cultured neurons and blocking oxidative stress [102]. HO-1 has been shown to have anti-apoptotic effect. On the other hand phytochemicals can also block the expression of various well-known proapoptotic genes encoding Bax/Bad, cyclin-dependent kinase inhibitor p21, caspase-1, and TNF-linked apoptosis-inducing ligand [103].

## 5. Induction of the Neurotrophic Factor Expression and Their Receptors by Natural Products

In healthy individuals, coffee fruit extracts elevate plasma BDNF concentrations [104]. In females with premenstrual disorder, curcumin triggers the upregulation of serum BDNF concentrations and improves ailment [105]. The elevated expression of various NTFs and BDNF by phytochemicals (Figure 3) in cellular as well as animal experiments are appraised in Table 1. GDNF is induced by smilagenin [106] and catalpol [107] in an animal experiment of PD, in a rat model of EGCG-induced spinal cord damage [108], and a mouse model of hesperidin-induced depression [109].

Zhang et al. [135] found that chronic curcumin treatments activate ERK or N-methyl-D-aspartate-CREB signaling, accelerate the expression of BDNF, and enhance pathological, biochemical, and behavioral changes in an AD rat model induced by ventricular inoculation of A$\beta_{1\text{-}42}$. An established antidepressant used in China called Xiao Chai Hu Tang (i.e., Minor Bupleurum Decoction) enhances the expression of NGF, BDNF, TrkA, and TrkB in a rat hippocampus of chronic mild stress [136]. In mouse, administration of olive polyphenols accelerates the expression of TrkB and TrkA, GDNF, and NGF in the olfactory bulbs and hippocampus, but not in the frontal cortex and striatum [137]. A Chinese herb, *Rehmannia glutinous* Libosch. used for the dementia, elevates GDNF mRNA in primary cortical astrocytes and C6 cells [138]. In the hippocampus, the initiation of TrkB, TrkA, and BDNF expressions is related to the antidepressant effects of phytochemicals via the progression of adult neurogenesis [139]. Flavonoids activate BDNF both in vitro and in vivo; however, GDNF is mainly activated by catalpol, resveratrol, curcumin, and various nonflavonoids. Flavonoids might enhance cognition, memory, as well as depression, while curcumin and resveratrol improve neuronal stress and inhibit apoptosis in AD and PD animal models. Besides, in cell line experiments, ginkgolides, EGCG, and curcumin derivatives accelerate the expression of BDNF in U118MG glioma cells more significantly than in SH-SY5Y neuroblastoma cells, advocating that glioblastoma cells may play crucial roles in the initiation of BDNF gene using phytochemicals [140].

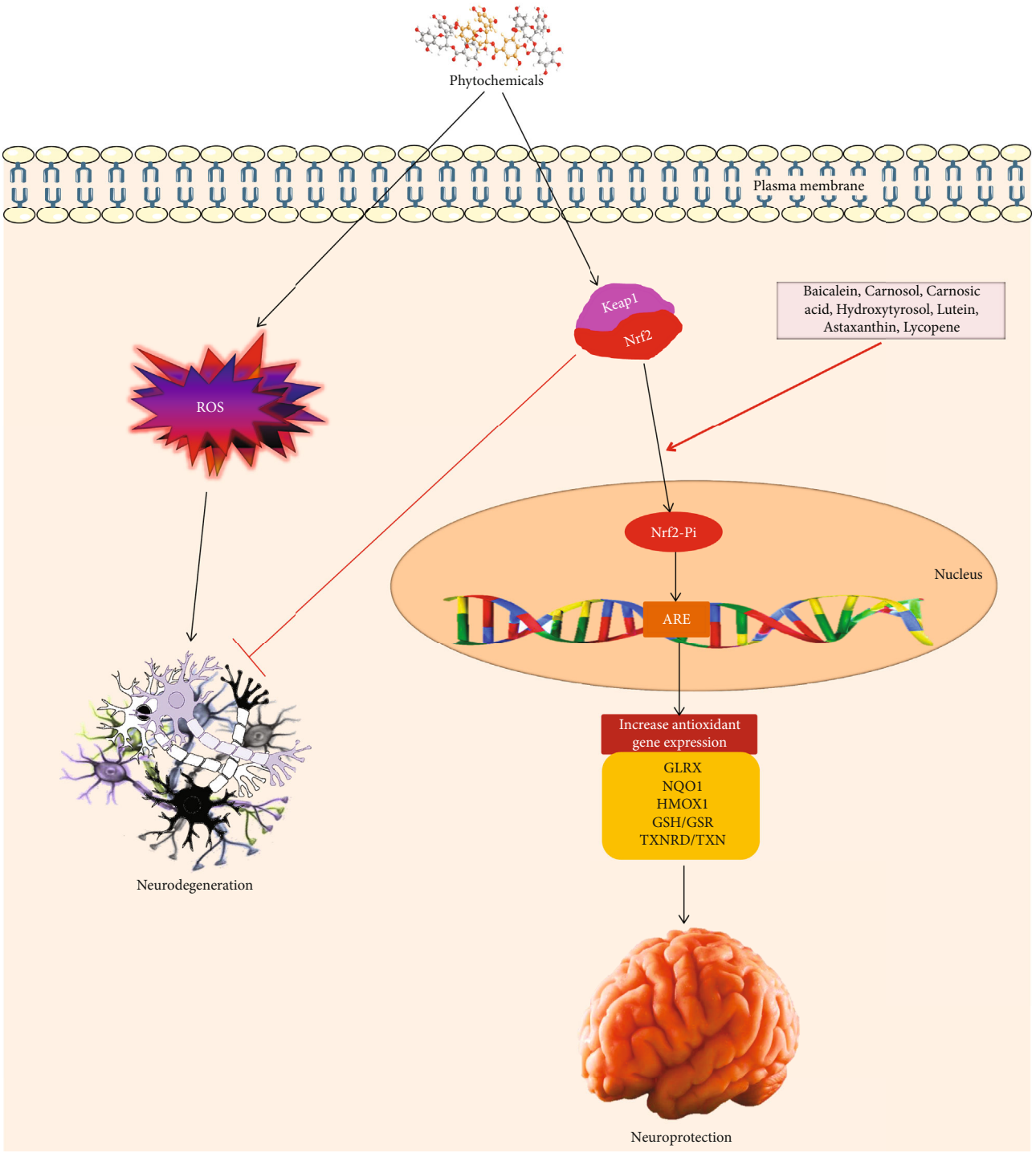


Figure 2: Phytochemicals activate the Keap-Nrf2-antioxidant response element cascade to increase the expression of antioxidant enzymes that fight against neurodegeneration.

## 6. Activation of Other Neurotrophic Pathways by Natural Products

Polyphenols that have numerous valuable functions in the nervous system offer a significant resource for the advancement of novel therapeutics for controlling NDs [141, 142]. Apart from the aforementioned signaling cascades associated with polyphenol-based neurotrophic effects, several other pathways might also be involved. Daidzein activity has resulted in substantial axonal development through the overexpression of the growth-associated protein (GAP)-43 in hippocampal neuronal cell cultures. Remarkably, daidzein-induced phosphorylation of GAP-43 and PKC has been removed by pretreatment with the endoplasmic reticulum

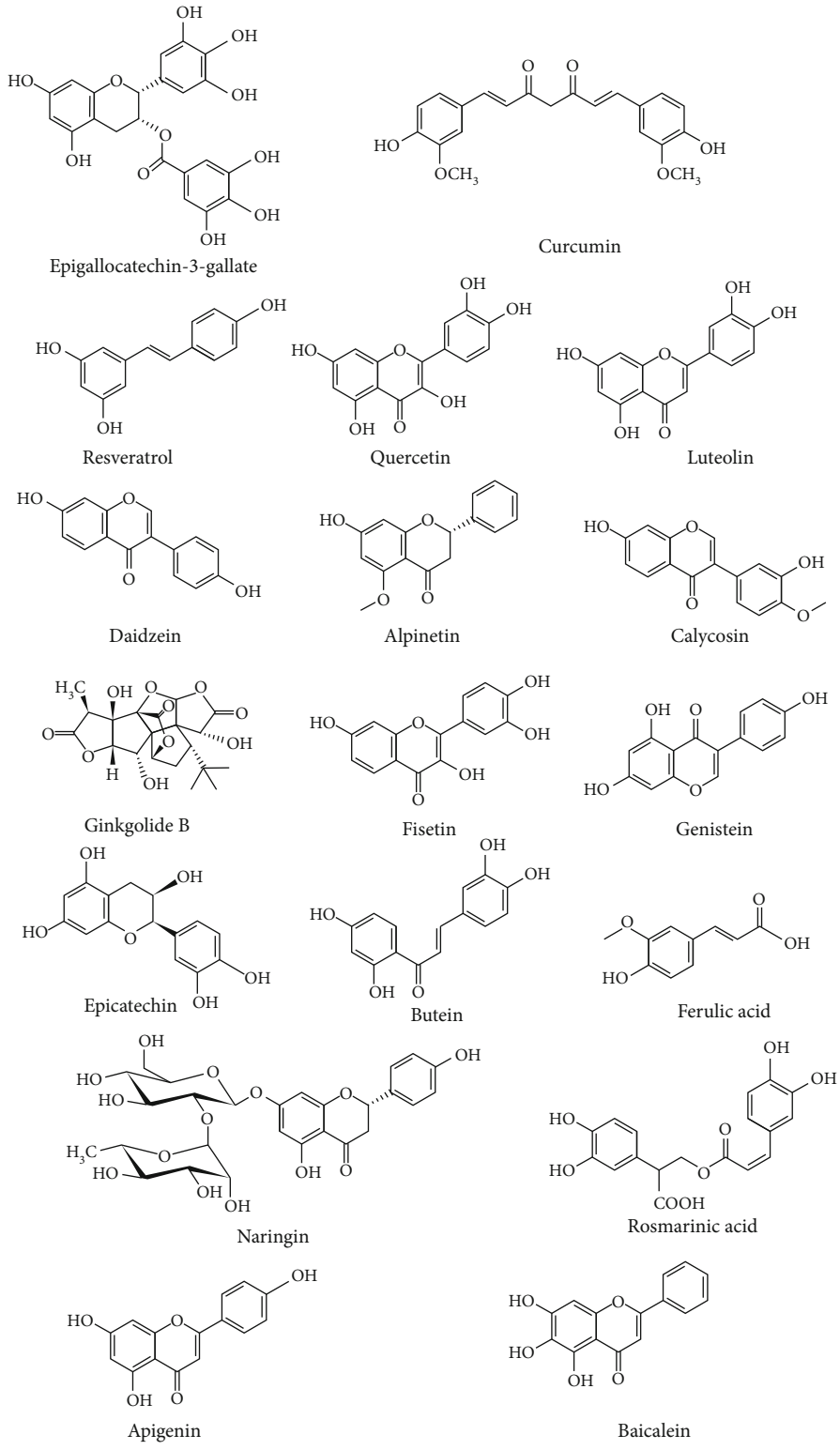


Figure 3: Chemical structures of the several phytochemicals that modulate the neurotrophic signals to attenuate neurodegeneration.

(ER) as well as PKC antagonist. These analyses advocate that ER-induced PKC phosphorylation of GAP-43 may perform a pivotal role in daidzein-prompted axonal development [143]. Similarly, hesperetin can show diverse neurotrophic actions through TrkA- and ER-prompted parallel pathways [144].

The $Na^+/K^+/2Cl^-$ cotransporter (NKCC) belongs to a member of the cation-chloride cotransporter family, which is involved in the passage of chloride ion(s) together with cation(s) through the plasma membrane [145]. Another experimental analysis has demonstrated that NGF-treated

Table 1: Promising studies regarding neurotrophic signals modulating potential of phytochemicals against neurodegeneration.

| Phytochemicals | Species/studied material | Experimental model | Dose | Therapeutic uses | Mechanisms | Induced Neurotrophins | References |
|---|---|---|---|---|---|---|---|
| Epigallocatechin-3-gallate | C57BL/6 mice | Sevoflurane-induced neurotoxicity | 25, 50, or 75 mg/kg | Neuroprotection | Activates CREB/BDNF/TrkB and PI3K/Akt/mTOR signalling pathway | BDNF | [110] |
| | Rats | Acrylamide-induced neurotoxicity | 10 mg/kg | Neuroprotection | Enhances acetylcholinesterase activity and reduces the expression of iNOS and COX-2 level | BDNF | [111] |
| | Sprague–Dawley rats | Spinal cord injury | 10 and 20 mg/kg | Neuroprotection | Upregulation of BDNF and GDNF | BDNF, GDNF | [112] |
| | PC12 cells | Oxidative-radical-stress-induced apoptosis | 0, 50, 100, 150 or, 200 $\mu$M | Neurodegenerative disorders | Activates PI3K/Akt and inhibits GSK-3 | NGF | [113] |
| | Rats | Stress-induced damage to hippocampal neurons | 5, 10, and 20 mg/kg | Enhances hippocampal neurogenesis | Upregulation of 5-HT(1A) receptors and BDNF | BDNF | [80]. |
| | Male Sprague–Dawley (SD) rats | 6-OHDA-induced Parkinson's disease | 5, 10, and 20 mg/kg | Neural regeneration and neuroprotection | Activates Trk/PI3K signaling pathways | BDNF | [71] |
| Curcumin | C57BL mice | MPTP-induced mice | 0.5% or 2.0% (w/w) | Neuroprotective effect | Increases expression of GDNF and TGF$\beta$1 | GDNF | [114] |
| | Rats | A$\beta$-induced cognitive impairments | 50 and 2.5 mg/kg | Improves cognitive deficit and neuroprotection | Activates PI3K/Akt signaling pathways and inhibits GSK-3 | BDNF | [115] |
| | Adult and aged mice | D-galactose-induced | 300 mg/kg | Improves cognitive impairment | Activates CREB signaling in the hippocampal dentate gyrus | BDNF | [116] |
| | Rodent cortical neurons | | 5 and 10 $\mu$M | Neuroprotection | Mediates through BDNF/TrkB-MAPK/PI-3 K-CREB signaling pathway | BDNF | [63] |
| | Adult Wistar rats | Two-vessel occlusion | 20 mg/kg | Neuritogenesis, neuroinflammation, and neuroprotection | Activates ERK-mediated CREB regulation, induces BDNF, NGF, and GDNF secretion, and inhibits IL10, IL-1$\beta$, and NF-$\kappa$B levels | BDNF and NGF | [117] |
| | Female Wistar rats | Dopaminergic neurons | 25–100 $\mu$M | Produces neurotrophic effects | Promotes the release of neurotrophic factors | BDNF and GDNF | [118] |
| Resveratrol | Female Wistar rats | Astroglia-enriched cultures | 25-100 $\mu$mmol/L | Neurological diseases | Induces the phosphorylation of (ERK1/2) andCREB in astroglia | BDNF and GDNF | [119]. |
| | Male Wistar rats | Chronic unpredictable mild stress-induced behavioral abnormalities | 20, 40 and 80 mg/kg | Antidepressant-like effects | Upregulates pERK, pCREB, and BDNF levels in the hippocampus and amygdala | BDNF | [120] |
| | Male Wistar rats | Phenylephrine-induced contraction of vascular smooth muscle cells | 10 mg/kg | Neuroprotection | Increases BDNF serum concentrations and reduces the contractility of resistance arteries via NOS-3-independent mechanisms | BDNF | [121] |
| Quercetin | Male Chinese Kunming mice | High-fat diet | 8.5 and 17 mg/kg | Improves cognitive impairment | Modulates PI3K/AKT/Nrf2 pathway and activates CREB pathway | BDNF | [122] |

Table 1: Continued.

| Phytochemicals | Species/studied material | Experimental model | Dose | Therapeutic uses | Mechanisms | Induced Neurotrophins | References |
|---|---|---|---|---|---|---|---|
| | Adult male Sprague Dawley rat | Hypobaric hypoxia-induced memory deficit | 50, 75 or 100 mg/kg | Ameliorates cognitive impairment | Regulates the expression of sirtuin 1, PGC-1$\alpha$, and the proteins related with mitochondrial biogenesis and dynamics | BDNF | [123]. |
| | Male Wistar albino rats | Streptozotocin-induced diabetes model | 50 mg/kg | Neuroprotection | Akt survival pathway, enhances the level of TrkB and Bcl-2, and reduces the level of both cytochrome c and caspase-3 | BDNF and NGF | [124] |
| | Adult male albino rats | Polychlorinated biphenyls-induced neurotoxicity | 50 mg/kg | Protects and prevents neuronal damage | Prevents transmembrane tight junctional proteins and cytoplasmic accessory tight junctional proteins in the hippocampus and keeps the level of estradiol | BDNF | [125] |
| Daidzein | H19-7/IGF-IR neural cell line | | 20 nM -2000 nM | Neuroprotection | Blocks a selective Trk receptors inhibitor, K252a | BDNF | [126] |
| Alpinetin, luteolin, calycosin, isohamnerin | Primary rat astrocytes | | 10 $\mu$M | Improves neurodegenerative diseases | Triggers estrogen signaling | BDNF, GDNF and NGF | [85] |
| Ginkgolide B | Cultured hippocampal neurons | A$\beta_{25-35}$ -induced apoptosis | 40 $\mu$g/ml | Neuroprotection | Upregulates BDNF | BDNF | [127] |
| Naringin | Sprague-Dawley rats | Spinal cord injury | 20 and 40 mg/kg | Neuroprotection | Upregulates BDNF and VEGF and the inhibits the neural apoptosis | BDNF and VEGF | [128] |
| Genistein | Primary rat astrocytes | | 10 $\mu$M | Improves neurodegenerative diseases | Triggers estrogen signaling | BDNF, GDNF and NGF | [85] |
| | H19-7/IGF-IR neural cell line | | 20 nM -2000 nM | Neuroprotection | Blocks a selective Trk receptors inhibitor, K252a | BDNF | [126] |
| Butein, fisetin | Mice | Glutamate-induced neurotoxicity | 40 mg/kg | Enhances cognitive effects | Inhibits iNOS and COX-2 and reactivates CREB-BDNF pathway | BDNF | [129] |
| Apigenin | Mice | MPTP-induced Parkinson's disease mice | 5, 10 and 20 mg/kg | Treatment of Parkinson's disease | Reduces oxidative damage, neuroinflammation, and microglial activation | BDNF | [130] |
| Epicatechin | Male C57BL/6 J mice | Hippocampus of anxiety mice | 4 mg/day | Treatment of mood disorders | Modulates monoaminergic and neurotrophic systems | BDNF | [131] |
| Rosmarinic acid | Sprague-Dawley rats | Chronic unpredictable stress | 10 mg/kg | Improves depressive-like behaviors | Alters in ERK1/2 signaling | BDNF | [132] |
| Baicalein | Mice | Chronic unpredictable mild stress | 1, 2, and 4 mg/kg | Treatment of depression | Triggers ERK-mediated neurotrophic action | BDNF | [133]. |
| Ferulic acid | Mice | Corticosterone-induced | 50, 100, or 250 mg/kg | Treatment of mood disorders | Increases CREB phosphorylation and BDNF mRNA level in the hippocampus | BDNF | [134]. |

PC12D cells overexpressed the NKCC1 protein [146]. Copious studies revealed that NKCC1 knockdown intensely prevents NGF mediated-neurite development in PC12 cells. Remarkably, quercetin also stimulated NGF-prompted neurite development by rising $Cl^-$ ion levels, though NKCC1 knockdown suppressed this stimulation. In PC12 cells, the intracellular chloride ion level influences microtubule polymerization through alteration of the inherent GTPase activity of tubulin [147].

A subclass of adenosine receptors A2A was demonstrated to increase the BDNF expression and the synaptic function of BDNF [148, 149]. Adenosine receptors also activate the TrkB receptor as well as the Akt pathway that prompts neuronal cell persistence and controls neurite development in various cell types [150–152]. Recently, Jeon et al. [153] revealed that oroxylin A might trigger BDNF outgrowth in cortical neurons through the stimulation of the A2A receptor that mediates neurite development, synapse formation, and cellular survival. In a subsequent study, the adenosine A2A receptor inhibitor was shown to inhibit methyl 3,4-dihydroxybenzoate-mediated neurite development as well as neuronal survival in primary cultures of cortical neurons [154].

## 7. Inhibition of Neurotoxin-Induced Damage by Natural Products and Associated Neurotrophic Signaling

Experimental analyses have shown that A$\beta$ is an essential factor in AD pathogenesis [155, 156]. Numerous data propose that several polyphenols prevent neuronal cells from A$\beta$ mediated neuronal damage or cell death. For example, icaritin has been revealed to defend primary rat cortical neuronal cells from apoptosis mediated by $A\beta_{25\text{-}35}$ insults [157]. Also, Ushikubo et al. [158] showed that 3,3′,4′,5,5′-pentahydroxyflavone prevents the deposition of A$\beta$ fibrils and that reducing fibril deposition and declines A$\beta$-mediated cell death in rat hippocampal neuronal cells. In an alternative analysis, p-coumaric acid, gallic acid, and ursolic acid isolated from Japanese *Cornus officinalis* Sieb. et Zucc. were proven to diminish proapoptotic functions including changes of nuclear morphology, deoxyribonucleic acid division, and A$\beta$-mediated cell blebbing in PC12 cells [159]. The primary flavonoids of cocoa, catechin, and epicatechin defend PC12 cells against A$\beta$-mediated neurotoxicity [160].

The flavonoid liquiritin and a bioactive phenolic compound (carnosic acid), extracted from *Rosemary*, display protection against A$\beta$ in primary cultures of hippocampal neurons and SH-SY5Y human neuroblastoma cells, respectively [161, 162]. 6-Hydroxydopamine (6-OHDA) is a neurotoxic synthetic organic compound that triggers pathology-like PD both in cellular and animal models. The trihydroxyflavone baicalein [163], caffeic acid derivatives, and ferulic acid [164] defend SH-SY5Y neuronal cells against 6-OHDA-induced neurotoxicity. Upon experimental analyses, ROS and hydrogen peroxide have been shown to stimulate neuronal cell injury [165]. In this case, numerous polyphenols including 7,8-DHF in RGC-5 and retinal ganglion cells (RGCs) [166], caffeic acid esters in PC12 cells [167], and quercetin in cultivated neuronal ancestor cells [168] are providing protection against ROS. Moreover, other researchers have proposed that the neuroprotective functions of 7,8-DHF are induced by its capacity to enhance the levels of cellular glutathione [169] by scavenging ROS.

Additional neurotoxins have also been employed to set up investigational trials to evaluate the neuroprotective capability of polyphenolic compounds. Caffeic acid phenethyl ester (CAPE) prevents PC12 cells from dopaminergic neurotoxin 1-methyl-4-phenylpyridinium [170]. In the mouse brain, administration of 7,8-DHF decreases neuronal cell death stimulated by kainic acid [61]. Icariin, another diglycosylated polyphenolic compound derived from kaempferol, can protect a primary culture of rat hippocampal neuronal cells from corticosterone-mediated death [171]. Similarly, baicalein has been demonstrated to block necrotic cell death injury in nasopharyngeal carcinomas (NPCs) and to reduce the loss of radiation-induced hippocampal neurogenesis [172]. Polyphenols also revealed beneficial effects in animal experiments of NDs triggered by diverse neurotoxins. Oral intake of luteolin alleviates memory and learning dysfunctions, in an A$\beta$-stimulated mice model of amnesia [173]. Curcumin, derived from *Curcuma longa* L., has also been demonstrated to be efficient in inhibiting tau hyperphosphorylation, neuroinflammation, and behavioral damages, induced by A$\beta$ in vivo [115].

## 8. Conclusion

The cellular mechanisms underlying the neuroprotective activity of phytochemicals must be elucidated to uncover a novel approach for developing drugs that able to interfere in the deterioration of brain activity in aging and age-related NDs. Mounting evidence recommends that enough attention should be paid towards clinical trials including these compounds. Therefore, it is essential to confirm the neuroprotective effects of these phytochemicals in various preclinical models and humans.

## Conflicts of Interest

The authors proclaim no competing interests.

## Authors' Contributions

MSU conceived of the original idea and designed the outlines of the study. MSU, AAM, and MMR wrote the draft of the manuscript. MSU and AAM prepared the figures for the manuscript. PJ and AA edited the whole manuscript and improved the draft. TB, MSS, ES-S, GMA, AAS, GMA, IP, and MMA-D performed the literature review and aided in revising the manuscript. All authors have read and agreed to the published version of the manuscript.

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## References


[1] R. C. Brown, A. H. Lockwood, and B. R. Sonawane, "Neurodegenerative diseases: an overview of environmental risk factors," *Environmental Health Perspectives*, vol. 113, no. 9, pp. 1250–1256, 2005.

[2] M. S. Uddin, A. Al Mamun, M. Asaduzzaman et al., "Spectrum of disease and prescription pattern for outpatients with neurological disorders: an empirical pilot study in Bangladesh," *Annals of Neurosciences*, vol. 25, no. 1, pp. 25–37, 2018.

[3] WHO, "Dementia: number of people affected to triple in next 30 years," March 2021, https://www.who.int/news/item/07-12-2017-dementia-number-of-people-affected-to-triple-in-next-30-years.

[4] M. F. Beal, A. E. Lang, and A. C. Ludolph, "Neurodegenerative diseases: neurobiology, pathogenesis and therapeutics," *Neurodegener. Dis. Neurobiol. Pathog. Ther.*, vol. 77, p. 284, 2005.

[5] M. S. Uddin, A. Al Mamun, M. Jakaria et al., "Emerging promise of sulforaphane-mediated Nrf2 signaling cascade against neurological disorders," *Science of the Total Environment*, vol. 707, p. 135624, 2020.

[6] C. W. Zhu and M. Sano, "Economic considerations in the management of Alzheimer's disease," *Clinical Interventions in Aging*, vol. 1, no. 2, pp. 143–154, 2006.

[7] E. Koca, O. Taskapilioglu, and M. Bakar, "Caregiver burden in different stages of Alzheimer's disease," *Noro Psikiyatri Arsivi*, vol. 54, no. 1, pp. 82–86, 2017.

[8] T. Finkel, "Signal transduction by reactive oxygen species," *The Journal of Cell Biology*, vol. 194, no. 1, pp. 7–15, 2011.

[9] M. S. Uddin, M. F. Hossain, A. Al Mamun et al., "Exploring the multimodal role of phytochemicals in the modulation of cellular signaling pathways to combat age-related neurodegeneration," *Science of the Total Environment*, vol. 725, p. 138313, 2020.

[10] B. Winner, Z. Kohl, and F. H. Gage, "Neurodegenerative disease and adult neurogenesis," *The European Journal of Neuroscience*, vol. 33, no. 6, pp. 1139–1151, 2011.

[11] M. S. Uddin and M. T. Kabir, "Oxidative stress in Alzheimer's disease: molecular hallmarks of underlying vulnerability," in *Biological, Diagnostic and Therapeutic Advances in Alzheimer's Disease*, pp. 91–115, Springer Singapore, Singapore, 2019.

[12] T. Nakamura and S. A. Lipton, "S-Nitrosylation and *u* ncompetitive/ *f* ast *o* ff-rate (UFO) drug therapy in neurodegenerative disorders of protein misfolding," *Cell Death and Differentiation*, vol. 14, no. 7, pp. 1305–1314, 2007.

[13] A. Al Mamun, M. S. Uddin, M. T. Kabir et al., "Exploring the promise of targeting ubiquitin-proteasome system to combat Alzheimer's disease," *Neurotoxicity Research*, vol. 38, no. 1, pp. 8–17, 2020.

[14] A. M. Weissmiller and C. Wu, "Current advances in using neurotrophic factors to treat neurodegenerative disorders," *Translational Neurodegeneration*, vol. 1, no. 1, p. 14, 2012.

[15] H. U. Saragovi, A. Galan, and L. A. Levin, "Neuroprotection: pro-survival and anti-neurotoxic mechanisms as therapeutic strategies in neurodegeneration," *Frontiers in Cellular Neuroscience*, vol. 13, 2019.

[16] K. H. Kim, M. A. Kim, E. Moon et al., "Furostanol saponins from the rhizomes of *Dioscorea japonica* and their effects on NGF induction," *Bioorganic & Medicinal Chemistry Letters*, vol. 21, no. 7, pp. 2075–2078, 2011.

[17] A. Konar, N. Shah, R. Singh et al., "Protective role of Ashwagandha leaf extract and its component withanone on scopolamine-induced changes in the brain and brain-derived cells," *PLoS One*, vol. 6, no. 11, article e27265, 2011.

[18] K. Schindowski, K. Belarbi, and L. Buée, "Neurotrophic factors in Alzheimer's disease: role of axonal transport," *Genes, Brain and Behavior*, vol. 7, Supplement 1, pp. 43–56, 2008.

[19] E. Palasz, A. Wysocka, A. Gasiorowska, M. Chalimoniuk, W. Niewiadomski, and G. Niewiadomska, "BDNF as a promising therapeutic agent in parkinson's disease," *International Journal of Molecular Sciences*, vol. 21, no. 3, p. 1170, 2020.

[20] S. S. Jiao, L. L. Shen, C. Zhu et al., "Brain-derived neurotrophic factor protects against tau-related neurodegeneration of Alzheimer's disease," *Translational Psychiatry*, vol. 6, no. 10, p. e907, 2016.

[21] K. Wan Woo, O. Wook Kwon, S. Yeou Kim et al., "Phenolic derivatives from the rhizomes of *Dioscorea nipponica* and their anti-neuroinflammatory and neuroprotective activities," *Journal of Ethnopharmacology*, vol. 155, no. 2, pp. 1164–1170, 2014.

[22] J. Hur, P. Lee, E. Moon et al., "Neurite outgrowth induced by spicatoside a, a steroidal saponin, via the tyrosine kinase a receptor pathway," *European Journal of Pharmacology*, vol. 620, no. 1-3, pp. 9–15, 2009.

[23] G. Kwon, H. E. Lee, D. H. Lee et al., "Spicatoside a enhances memory consolidation through the brain-derived neurotrophic factor in mice," *Neuroscience Letters*, vol. 572, pp. 58–62, 2014.

[24] G. Chen, K. A. Bower, M. Xu et al., "Cyanidin-3-Glucoside reverses ethanol-induced inhibition of neurite outgrowth: role of glycogen synthase kinase 3 Beta," *Neurotoxicity Research*, vol. 15, no. 4, pp. 321–331, 2009.

[25] S. Bawari, D. Tewari, S. Argüelles et al., "Targeting BDNF signaling by natural products: novel synaptic repair therapeutics for neurodegeneration and behavior disorders," *Pharmacological Research*, vol. 148, p. 104458, 2019.

[26] J. Y. Hur, P. Lee, H. Kim, I. Kang, K. R. Lee, and S. Y. Kim, "(−)-3,5-Dicaffeoyl-*muco*-quinic acid isolated from *Aster scaber* contributes to the differentiation of PC12 cells: through tyrosine kinase cascade signaling," *Biochemical and Biophysical Research Communications*, vol. 313, no. 4, pp. 948–953, 2004.

[27] D. Tewari, A. M. Stankiewicz, A. Mocan et al., "Ethnopharmacological approaches for dementia therapy and significance of natural products and herbal drugs," *Frontiers in Aging Neuroscience*, vol. 10, 2018.

[28] Z. J. Wang, B. M. Nie, H. Z. Chen, and Y. Lu, "Panaxynol induces neurite outgrowth in PC12D cells via *c* AMP- and MAP kinase-dependent mechanisms," *Chemico-Biological Interactions*, vol. 159, no. 1, pp. 58–64, 2006.

[29] V. Karpagam, N. Sathishkumar, S. Sathiyamoorthy et al., "Identification of BACE1 inhibitors from *Panax ginseng* saponins –An Insilco approach," *Computers in Biology and Medicine*, vol. 43, no. 8, pp. 1037–1044, 2013.

[30] E. Castrén and H. Antila, "Neuronal plasticity and neurotrophic factors in drug responses," *Molecular Psychiatry*, vol. 22, no. 8, pp. 1085–1095, 2017.

[31] C. Lanni, S. Stanga, M. Racchi, and S. Govoni, "The expanding universe of neurotrophic factors: therapeutic potential in

aging and age-associated disorders," *Current Pharmaceutical Design*, vol. 16, no. 6, pp. 698–717, 2010.

[32] M. Barbacid, "The Trk family of neurotrophin receptors," *Journal of Neurobiology*, vol. 25, no. 11, pp. 1386–1403, 1994.

[33] R. Levi-Montalcini, "The nerve growth factor: thirty-five years later," *Bioscience Reports*, vol. 7, no. 9, pp. 681–699, 1987.

[34] L. F. Reichardt, "Neurotrophin-regulated signalling pathways," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 361, no. 1473, pp. 1545–1564, 2006.

[35] M. Nibuya, S. Morinobu, and R. S. Duman, "Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments," *The Journal of Neuroscience*, vol. 15, no. 11, pp. 7539–7547, 1995.

[36] L. Lei and L. F. Parada, "Transcriptional regulation of Trk family neurotrophin receptors," *Cellular and Molecular Life Sciences*, vol. 64, no. 5, pp. 522–532, 2007.

[37] J. Hur, P. Lee, J. Kim, A. J. Kim, H. Kim, and S. Y. Kim, "Induction of nerve growth factor by butanol fraction of Liriope platyphylla in C6 and primary astrocyte cells," *Biological & Pharmaceutical Bulletin*, vol. 27, no. 8, pp. 1257–1260, 2004.

[38] M. Korte, P. Carroll, E. Wolf, G. Brem, H. Thoenen, and T. Bonhoeffer, "Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 92, no. 19, pp. 8856–8860, 1995.

[39] R. A. Segal and M. E. Greenberg, "Intracellular signaling pathways activated by Neuropathic factors," *Annual Review of Neuroscience*, vol. 19, no. 1, pp. 463–489, 1996.

[40] X. Gao, R. L. Daugherty, and W. G. Tourtellotte, "Regulation of low affinity neurotrophin receptor ($p75^{NTR}$) by early growth response (Egr) transcriptional regulators," *Molecular and Cellular Neurosciences*, vol. 36, no. 4, pp. 501–514, 2007.

[41] R. S. Kenchappa, C. Tep, Z. Korade et al., "p75 Neurotrophin receptor-mediated apoptosis in sympathetic neurons involves a biphasic activation of JNK and up-regulation of tumor necrosis factor-$\alpha$- converting enzyme/ADAM17," *The Journal of Biological Chemistry*, vol. 285, no. 26, pp. 20358–20368, 2010.

[42] M. Vilar, I. Charalampopoulos, R. S. Kenchappa et al., "Activation of the p75 neurotrophin receptor through conformational rearrangement of disulphide-linked receptor dimers," *Neuron*, vol. 62, no. 1, pp. 72–83, 2009.

[43] Q. Qu, J. Chen, Y. Wang et al., "Structural Characterization of the Self-Association of the Death Domain of p75NTR," *PLoS One*, vol. 8, no. 3, article e57839, 2013.

[44] R. Venkatesan, E. Ji, and S. Y. Kim, "Phytochemicals that regulate neurodegenerative disease by targeting neurotrophins: a comprehensive review," *BioMed Research International*, vol. 2015, Article ID 814068, 22 pages, 2015.

[45] S. Descamps, R. A. Toillon, E. Adriaenssens et al., "Nerve Growth Factor Stimulates Proliferation and Survival of Human Breast Cancer Cells through Two Distinct Signaling Pathways," *The Journal of Biological Chemistry*, vol. 276, no. 21, pp. 17864–17870, 2001.

[46] S. Mitra, H. Behbahani, and M. Eriksdotter, "Innovative therapy for Alzheimer's disease-with focus on biodelivery of NGF," *Frontiers in Neuroscience*, vol. 13, 2019.

[47] C. J. Xu, J. L. Wang, and W. L. Jin, "The emerging therapeutic role of NGF in Alzheimer's disease," *Neurochemical Research*, vol. 41, no. 6, pp. 1211–1218, 2016.

[48] D. Siniscalco, C. Giordano, F. Rossi, S. Maione, and V. de Novellis, "Role of neurotrophins in neuropathic pain," *Current Neuropharmacology*, vol. 9, no. 4, pp. 523–529, 2011.

[49] S. Pilakka-Kanthikeel, V. S. R. Atluri, V. Sagar, S. K. Saxena, and M. Nair, "Targeted brain derived neurotropic factors (BDNF) delivery across the blood-brain barrier for neuroprotection using magnetic nano carriers: an in-vitro study," *PLoS One*, vol. 8, no. 4, p. e62241, 2013.

[50] Y. Xing, C. Y. Wen, S. T. Li, and Z. X. Xia, "Non-viral liposome-mediated transfer of brain-derived neurotrophic factor across the blood-brain barrier," *Neural Regeneration Research*, vol. 11, no. 4, pp. 617–622, 2016.

[51] A. Whone, M. Luz, M. Boca et al., "Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease," *Brain*, vol. 142, no. 3, pp. 512–525, 2019.

[52] ClinicalTrials.gov, "GDNF gene therapy for Parkinson's disease".

[53] J. Hunsberger, D. R. Austin, I. D. Henter, and G. Chen, "The neurotrophic and neuroprotective effects of psychotropic agents," *Dialogues in Clinical Neuroscience*, vol. 11, no. 3, pp. 333–348, 2009.

[54] K. Hisaoka, A. Nishida, T. Koda et al., "Antidepressant drug treatments induce glial cell line-derived neurotrophic factor (GDNF) synthesis and release in rat C6 glioblastoma cells," *Journal of Neurochemistry*, vol. 79, no. 1, pp. 25–34, 2001.

[55] K. Ohta, S. Kuno, S. Inoue, E. Ikeda, A. Fujinami, and M. Ohta, "The effect of dopamine agonists: the expression of GDNF, NGF, and BDNF in cultured mouse astrocytes," *Journal of the Neurological Sciences*, vol. 291, no. 1–2, pp. 12–16, 2010.

[56] Y. Sagi, S. Mandel, T. Amit, and M. B. H. Youdim, "Activation of tyrosine kinase receptor signaling pathway by rasagiline facilitates neurorescue and restoration of nigrostriatal dopamine neurons in post-MPTP-induced parkinsonism," *Neurobiology of Disease*, vol. 25, no. 1, pp. 35–44, 2007.

[57] I. Semkova, P. Wolz, M. Schilling, and J. Krieglstein, "Selegiline enhances NGF synthesis and protects central nervous system neurons from excitotoxic and ischemic damage," *European Journal of Pharmacology*, vol. 315, no. 1, pp. 19–30, 1996.

[58] M. Naoi, W. Maruyama, and M. Shamoto-Nagai, "Rasagiline and selegiline modulate mitochondrial homeostasis, intervene apoptosis system and mitigate $\alpha$-synuclein cytotoxicity in disease-modifying therapy for Parkinson's disease," *Journal of Neural Transmission*, vol. 127, no. 2, pp. 131–147, 2020.

[59] M. Naoi, W. Maruyama, and K. Inaba-Hasegawa, "Revelation in the neuroprotective functions of rasagiline and selegiline: the induction of distinct genes by different mechanisms," *Expert Review of Neurotherapeutics*, vol. 13, no. 6, pp. 671–684, 2013.

[60] I. Figueira, R. Menezes, D. Macedo, I. Costa, and C. N. dos Santos, "Polyphenols beyond barriers: a glimpse into the brain," *Current Neuropharmacology*, vol. 15, no. 4, pp. 562–594, 2017.

[61] S. W. Jang, X. Liu, M. Yepes et al., "A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone,"

*Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 6, pp. 2687–2692, 2010.

[62] C. Liu, C. B. Chan, and K. Ye, "7,8-dihydroxyflavone, a small molecular TrkB agonist, is useful for treating various BDNF-implicated human disorders," *Translational Neurodegeneration*, vol. 5, no. 1, 2016.

[63] R. Wang, Y. H. Li, Y. Xu et al., "Curcumin produces neuroprotective effects via activating brain-derived neurotrophic factor/TrkB-dependent MAPK and PI-3K cascades in rodent cortical neurons," *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, vol. 34, no. 1, pp. 147–153, 2010.

[64] T. Shibata, H. Nakahara, N. Kita et al., "A food-derived synergist of NGF signaling: identification of protein tyrosine phosphatase 1B as a key regulator of NGF receptor-initiated signal transduction," *Journal of Neurochemistry*, vol. 107, no. 5, pp. 1248–1260, 2008.

[65] S. W. Jang, M. Okada, I. Sayeed et al., "Gambogic amide, a selective agonist for TrkA receptor that possesses robust neurotrophic activity, prevents neuronal cell death," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 41, pp. 16329–16334, 2007.

[66] M. M. H. al-Gayyar, S. Matragoon, B. A. Pillai, T. K. Ali, M. A. Abdelsaid, and A. B. el-Remessy, "Epicatechin blocks pro-nerve growth factor (proNGF)-mediated retinal neurodegeneration via inhibition of p75 neurotrophin receptor proNGF expression in a rat model of diabetes," *Diabetologia*, vol. 54, no. 3, pp. 669–680, 2011.

[67] F. Xu, C. Wang, L. Yang et al., "*C*-dideoxyhexosyl flavones from the stems and leaves of *Passiflora edulis* Sims," *Food Chemistry*, vol. 136, no. 1, pp. 94–99, 2013.

[68] Y. Yang, L. Bai, X. Li et al., "Transport of active flavonoids, based on cytotoxicity and lipophilicity: an evaluation using the blood-brain barrier cell and Caco-2 cell models," *Toxicology In Vitro*, vol. 28, no. 3, pp. 388–396, 2014.

[69] L. Jia, J. Liu, Z. Song et al., "Berberine suppresses amyloid-beta-induced inflammatory response in microglia by inhibiting nuclear factor-kappaB and mitogen-activated protein kinase signalling pathways," *The Journal of Pharmacy and Pharmacology*, vol. 64, no. 10, pp. 1510–1521, 2012.

[70] P. Kuner, R. Schubenel, and C. Hertel, "?-amyloid binds to p75NTRand activates NF?B in human neuroblastoma cells," *Journal of Neuroscience Research*, vol. 54, no. 6, pp. 798–804, 1998.

[71] J. Yang, S. Song, J. Li, and T. Liang, "Neuroprotective effect of curcumin on hippocampal injury in 6-OHDA-induced Parkinson's disease rat," *Pathology, Research and Practice*, vol. 210, no. 6, pp. 357–362, 2014.

[72] R. W. Olsen and W. Sieghart, "GABAA receptors: subtypes provide diversity of function and pharmacology," *Neuropharmacology*, vol. 56, no. 1, pp. 141–148, 2009.

[73] J. R. Hanrahan, M. Chebib, and G. A. R. Johnston, "Flavonoid modulation of GABAAreceptors," *British Journal of Pharmacology*, vol. 163, no. 2, pp. 234–245, 2011.

[74] L. Ren, F. Wang, Z. Xu, W. M. Chan, C. Zhao, and H. Xue, "$GABA_A$ receptor subtype selectivity underlying anxiolytic effect of 6-hydroxyflavone," *Biochemical Pharmacology*, vol. 79, no. 9, pp. 1337–1344, 2010.

[75] K. M. Hui, M. S. Y. Huen, H. Y. Wang et al., "Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from *Scutellaria baicalensis* Georgi," *Biochemical Pharmacology*, vol. 64, no. 9, pp. 1415–1424, 2002.

[76] S. ali Shah, I. Ullah, H. Y. Lee, and M. O. Kim, "Anthocyanins protect against ethanol-induced neuronal apoptosis via GABAB1 receptors intracellular signaling in prenatal rat hippocampal neurons," *Molecular Neurobiology*, vol. 48, no. 1, pp. 257–269, 2013.

[77] J. Dai, L. Chen, Y. M. Qiu et al., "Activations of GABAergic signaling, HSP70 and MAPK cascades are involved in baicalin's neuroprotection against gerbil global ischemia/reperfusion injury," *Brain Research Bulletin*, vol. 90, pp. 1–9, 2013.

[78] L. L. Guo, Z. Z. Guan, and Y. L. Wang, "Scutellarin protects against A$\beta$-induced learning and memory deficits in rats: involvement of nicotinic acetylcholine receptors and cholinesterase," *Acta Pharmacologica Sinica*, vol. 32, no. 12, pp. 1446–1453, 2011.

[79] X. Zhang, M. Wu, F. Lu, N. Luo, Z. P. He, and H. Yang, "Involvement of $\alpha$7 nAChR signaling cascade in epigallocatechin gallate suppression of $\beta$-Amyloid-Induced apoptotic cortical neuronal insults," *Molecular Neurobiology*, vol. 49, no. 1, pp. 66–77, 2014.

[80] Y. Xu, B. Ku, L. Cui et al., "Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats," *Brain Research*, vol. 1162, no. 1, pp. 9–18, 2007.

[81] Y. Xu, S. Li, M. M. Vernon et al., "Curcumin prevents corticosterone-induced neurotoxicity and abnormalities of neuroplasticity via 5-HT receptor pathway," *Journal of Neurochemistry*, vol. 118, no. 5, pp. 784–795, 2011.

[82] L. Gu, Y. J. Liu, Y. B. Wang, and L. T. Yi, "Role for monoaminergic systems in the antidepressant-like effect of ethanol extracts from *Hemerocallis citrina*," *Journal of Ethnopharmacology*, vol. 139, no. 3, pp. 780–787, 2012.

[83] J. Yang, X. Wu, H. Yu, X. Liao, and L. Teng, "NMDA receptor-mediated neuroprotective effect of the scutellaria baicalensis georgi extract on the excitotoxic neuronal cell death in primary rat cortical cell cultures," *Scientific World Journal*, vol. 2014, article 459549, 8 pages, 2014.

[84] Q. G. Gao, W. F. Chen, J. X. Xie, and M. S. Wong, "Ginsenoside Rg1 protects against 6-OHDA-induced neurotoxicity in neuroblastoma SK-N-SH cells via IGF-I receptor and estrogen receptor pathways," *Journal of Neurochemistry*, vol. 109, no. 5, pp. 1338–1347, 2009.

[85] S. L. Xu, C. W. C. Bi, R. C. Y. Choi et al., "Flavonoids induce the synthesis and secretion of neurotrophic factors in cultured rat astrocytes: a signaling response mediated by estrogen receptor," *Evidence-based Complementary and Alternative Medicine*, vol. 2013, Article ID 127075, 10 pages, 2013.

[86] O. Firuzi, F. Moosavi, R. Hosseini, and L. Saso, "Modulation of neurotrophic signaling pathways by polyphenols," *Drug Design, Development and Therapy*, vol. 10, pp. 23–42, 2015.

[87] M. S. Uddin, M. T. Kabir, K. Niaz et al., "Molecular insight into the therapeutic promise of flavonoids against Alzheimer's disease," *Molbank*, vol. 25, no. 6, p. 1267, 2020.

[88] Y. Levites, T. Amit, M. B. H. Youdim, and S. Mandel, "Involvement of Protein Kinase C Activation and Cell Survival/ Cell Cycle Genes in Green Tea Polyphenol (−)-Epigallocatechin 3-Gallate Neuroprotective Action," *The Journal*

*of Biological Chemistry*, vol. 277, no. 34, pp. 30574–30580, 2002.

[89] S. Luo, T. Lan, W. Liao, M. Zhao, and H. Yang, "Genistein inhibits A$\beta$25-35 -induced neurotoxicity in PC12 cells via PKC signaling pathway," *Neurochemical Research*, vol. 37, no. 12, pp. 2787–2794, 2012.

[90] C. Menard, S. Bastianetto, and R. Quirion, "Neuroprotective effects of resveratrol and epigallocatechin gallate polyphenols are mediated by the activation of protein kinase C gamma," *Frontiers in Cellular Neuroscience*, vol. 7, 2013.

[91] M. S. Uddin and M. T. Kabir, "Emerging signal regulating potential of genistein against Alzheimer's disease: a promising molecule of interest," *Frontiers in Cell and Development Biology*, vol. 7, p. 197, 2019.

[92] B. N. Singh, S. Shankar, and R. K. Srivastava, "Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications," *Biochemical Pharmacology*, vol. 82, no. 12, pp. 1807–1821, 2011.

[93] K. Nakaso, S. Ito, and K. Nakashima, "Caffeine activates the PI3K/Akt pathway and prevents apoptotic cell death in a Parkinson's disease model of SH-SY5Y cells," *Neuroscience Letters*, vol. 432, no. 2, pp. 146–150, 2008.

[94] P. O. Koh, "Ferulic acid attenuates the down-regulation of MEK/ERK/p90RSK signaling pathway in focal cerebral ischemic injury," *Neuroscience Letters*, vol. 588, pp. 18–23, 2015.

[95] S. J. Vauzour, K. Vafeiadou, C. Rice-Evans, R. J. Williams, and J. P. E. Spencer, "Activation of pro-survival Akt and ERK1/2 signalling pathways underlie the anti-apoptotic effects of flavanones in cortical neurons," *Journal of Neurochemistry*, vol. 103, no. 4, pp. 1355–1367, 2007.

[96] L. J. Sharoni, M. Danilenko, N. Dubi, A. Ben-Dor, and J. Levy, "Carotenoids and transcription," *Archives of Biochemistry and Biophysics*, vol. 430, no. 1, pp. 89–96, 2004.

[97] C. Rendeiro, J. S. Rhodes, and J. P. E. Spencer, "The mechanisms of action of flavonoids in the brain: Direct *versus* indirect effects," *Neurochemistry International*, vol. 89, pp. 126–139, 2015.

[98] R.-E. C. Williams, J. P. E. Spencer, and C. Rice-Evans, "Flavonoids: antioxidants or signalling molecules?," *Free Radical Biology & Medicine*, vol. 36, no. 7, pp. 838–849, 2004.

[99] S. Qin, F. Deng, W. Wu et al., "Baicalein modulates Nrf2/Keap1 system in both Keap1-dependent and Keap1-independent mechanisms," *Archives of Biochemistry and Biophysics*, vol. 559, pp. 53–61, 2014.

[100] L. S. Satoh, S. R. McKercher, and S. A. Lipton, "Nrf2/ARE-mediated antioxidant actions of pro-electrophilic drugs," *Free Radical Biology & Medicine*, vol. 65, pp. 645–657, 2013.

[101] S. Peng, B. Zhang, J. Yao, D. Duan, and J. Fang, "Dual protection of hydroxytyrosol, an olive oil polyphenol, against oxidative damage in PC12 cells," *Food & Function*, vol. 6, no. 6, pp. 2091–2100, 2015.

[102] L. Romeo, M. Intrieri, V. D'Agata et al., "The major green tea polyphenol, (-)-epigallocatechin-3-gallate, induces heme oxygenase in rat neurons and acts as an effective neuroprotective agent against oxidative stress," *Journal of the American College of Nutrition*, vol. 28, Supplement 4, pp. 492S–499S, 2009.

[103] S. H. Kwon, J. A. Kim, S. I. Hong et al., "Loganin protects against hydrogen peroxide-induced apoptosis by inhibiting phosphorylation of JNK, p38, and ERK 1/2 MAPKs in SH-SY5Y cells," *Neurochemistry International*, vol. 58, no. 4, pp. 533–541, 2011.

[104] T. Reyes-Izquierdo, B. Nemzer, C. Shu et al., "Modulatory effect of coffee fruit extract on plasma levels of brain-derived neurotrophic factor in healthy subjects," *The British Journal of Nutrition*, vol. 110, no. 3, pp. 420–425, 2013.

[105] H. Fanaei, S. Khayat, A. Kasaeian, and M. Javadimehr, "Effect of curcumin on serum brain-derived neurotrophic factor levels in women with premenstrual syndrome: a randomized, double-blind, placebo-controlled trial," *Neuropeptides*, vol. 56, pp. 25–31, 2016.

[106] Y. Zhang, Z. Xia, Y. Hu, A. Orsi, and D. Rees, "Role of glial cell derived neurotrophic factor in the protective effect of smilagenin on rat mesencephalic dopaminergic neurons damaged by MPP+," *FEBS Letters*, vol. 582, no. 6, pp. 956–960, 2008.

[107] G. Xu, Z. Xiong, Y. Yong et al., "Catalpol attenuates MPTP induced neuronal degeneration of nigral-striatal dopaminergic pathway in mice through elevating glial cell derived neurotrophic factor in striatum," *Neuroscience*, vol. 167, no. 1, pp. 174–184, 2010.

[108] X. Han, N. Yang, Y. Xu et al., "Simvastatin treatment improves functional recovery after experimental spinal cord injury by upregulating the expression of BDNF and GDNF," *Neuroscience Letters*, vol. 38, no. 4, pp. 772–779, 2011.

[109] C. F. Li, S. M. Chen, X. M. Chen et al., "ERK-dependent brain-derived neurotrophic factor regulation by hesperidin in mice exposed to chronic mild stress," *Brain Research Bulletin*, vol. 124, pp. 40–47, 2016.

[110] M. L. Ding, H. Ma, Y. G. Man, and H. Y. LV, "Protective effects of a green tea polyphenol, epigallocatechin-3-gallate, against sevoflurane-induced neuronal apoptosis involve regulation of CREB/BDNF/TrkB and PI3K/Akt/mTOR signalling pathways in neonatal mice," *Canadian Journal of Physiology and Pharmacology*, vol. 95, no. 12, pp. 1396–1405, 2017.

[111] Y. He, D. Tan, Y. Mi, Q. Zhou, and S. Ji, "Epigallocatechin-3-gallate attenuates cerebral cortex damage and promotes brain regeneration in acrylamide-treated rats," *Food & Function*, vol. 8, no. 6, pp. 2275–2282, 2017.

[112] W. Tian, X. G. Han, Y. J. Liu et al., "Intrathecal epigallocatechin gallate treatment improves functional recovery after spinal cord injury by upregulating the expression of BDNF and GDNF," *Neurochemical Research*, vol. 38, no. 4, pp. 772–779, 2013.

[113] S.-H. Koh, S. H. Kim, H. Kwon et al., "Epigallocatechin gallate protects nerve growth factor differentiated PC12 cells from oxidative-radical-stress-induced apoptosis through its effect on phosphoinositide 3-kinase/Akt and glycogen synthase kinase-3," *Molecular Brain Research*, vol. 118, no. 1–2, pp. 72–81, 2003.

[114] X. J. He, K. Uchida, C. Megumi, N. Tsuge, and H. Nakayama, "Dietary curcumin supplementation attenuates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in C57BL mice," *Journal of Toxicologic Pathology*, vol. 28, no. 4, pp. 197–206, 2015.

[115] J. B. Hoppe, K. Coradini, R. L. Frozza et al., "Free and nanoencapsulated curcumin suppress $\beta$-amyloid-induced cognitive impairments in rats: involvement of BDNF and Akt/GSK-3$\beta$ signaling pathway," *Neurobiology of Learning and Memory*, vol. 106, pp. 134–144, 2013.

[116] S. M. Nam, J. H. Choi, D. Y. Yoo et al., "Effects of curcumin (Curcuma longa) on learning and spatial memory as well as

cell proliferation and neuroblast differentiation in adult and aged mice by upregulating brain-derived neurotrophic factor and CREB signaling," *Journal of Medicinal Food*, vol. 17, no. 6, pp. 641–649, 2014.

[117] J. R. Anastácio, C. A. Netto, C. C. Castro et al., "Resveratrol treatment has neuroprotective effects and prevents cognitive impairment after chronic cerebral hypoperfusion," *Neurological Research*, vol. 36, no. 7, pp. 627–633, 2014.

[118] F. Zhang, Y.-Y. Wang, H. Liu et al., "Resveratrol produces neurotrophic effects on cultured dopaminergic neurons through prompting astroglial BDNF and GDNF release," *Evidence-based Complementary and Alternative Medicine*, vol. 2012, Article ID 937605, 7 pages, 2012.

[119] F. Zhang, Y. F. Lu, Q. Wu, J. Liu, and J. S. Shi, "Resveratrol promotes neurotrophic factor release from astroglia," *Experimental Biology and Medicine*, vol. 237, no. 8, pp. 943–948, 2012.

[120] D. Liu, K. Xie, X. Yang et al., "Resveratrol reverses the effects of chronic unpredictable mild stress on behavior, serum corticosterone levels and BDNF expression in rats," *Behavioural Brain Research*, vol. 264, pp. 9–16, 2014.

[121] M. Wiciński, B. Malinowski, M. M. Węclewicz, E. Grześk, and G. Grześk, "Resveratrol increases serum BDNF concentrations and reduces vascular smooth muscle cells contractility via a NOS-3-independent mechanism," *BioMed Research International*, vol. 2017, Article ID 9202954, 7 pages, 2017.

[122] S. F. Xia, Z. X. Xie, Y. Qiao et al., "Differential effects of quercetin on hippocampus-dependent learning and memory in mice fed with different diets related with oxidative stress," *Physiology & Behavior*, vol. 138, pp. 325–331, 2015.

[123] P. Liu, D. Zou, L. Yi et al., "Quercetin ameliorates hypobaric hypoxia-induced memory impairment through mitochondrial and neuron function adaptation via the PGC-1$\alpha$ pathway," *Restorative Neurology and Neuroscience*, vol. 33, no. 2, pp. 143–157, 2015.

[124] M. S. Ola, M. M. Ahmed, S. Shams, and S. S. al-Rejaie, "Neuroprotective effects of quercetin in diabetic rat retina," *Saudi Journal of Biological Sciences*, vol. 24, no. 6, pp. 1186–1194, 2017.

[125] K. Selvakumar, S. Bavithra, G. Krishnamoorthy, and J. Arunakaran, "Impact of quercetin on tight junctional proteins and BDNF signaling molecules in hippocampus of PCBs-exposed rats," *Interdisciplinary Toxicology*, vol. 11, no. 4, pp. 294–305, 2018.

[126] M. Pan, H. Han, C. Zhong, and Q. Geng, "Effects of genistein and daidzein on hippocampus neuronal cell proliferation and bdnf expression in h19-7 neural cell line," *The Journal of Nutrition, Health & Aging*, vol. 16, no. 4, pp. 389–394, 2012.

[127] Q. Xiao, C. Wang, J. Li et al., "Ginkgolide B protects hippocampal neurons from apoptosis induced by beta- amyloid 25-35 partly via up-regulation of brain-derived neurotrophic factor," *European Journal of Pharmacology*, vol. 647, no. 1–3, pp. 48–54, 2010.

[128] W. Rong, J. Wang, X. Liu et al., "Naringin treatment improves functional recovery by increasing BDNF and VEGF expression, inhibiting neuronal apoptosis after spinal cord injury," *Neurochemical Research*, vol. 37, no. 8, pp. 1615–1623, 2012.

[129] N. Cho, K. Y. Lee, J. Huh et al., "Cognitive-enhancing effects of *Rhus verniciflua* bark extract and its active flavonoids with neuroprotective and anti-inflammatory activities," *Food and Chemical Toxicology*, vol. 58, pp. 355–361, 2013.

[130] S. P. Patil, P. D. Jain, J. S. Sancheti, P. J. Ghumatkar, R. Tambe, and S. Sathaye, "Neuroprotective and neurotrophic effects of apigenin and luteolin in MPTP induced parkinsonism in mice," *Neuropharmacology*, vol. 86, pp. 192–202, 2014.

[131] T. P. Stringer, D. Guerrieri, C. Vivar, and H. van Praag, "Plant-derived flavanol (−)epicatechin mitigates anxiety in association with elevated hippocampal monoamine and BDNF levels, but does not influence pattern separation in mice," *Translational Psychiatry*, vol. 5, no. 1, p. e493, 2015.

[132] X. Jin, P. Liu, F. Yang, Y. H. Zhang, and D. Miao, "Rosmarinic acid ameliorates depressive-like behaviors in a rat model of CUS and up-regulates BDNF levels in the hippocampus and hippocampal-derived astrocytes," *Neurochemical Research*, vol. 38, no. 9, pp. 1828–1837, 2013.

[133] Z. Xiong, B. Jiang, P. F. Wu et al., "Antidepressant effects of a plant-derived flavonoid baicalein involving extracellular signal-regulated kinases cascade," *Biological & Pharmaceutical Bulletin*, vol. 34, no. 2, pp. 253–259, 2011.

[134] T. Yabe, H. Hirahara, N. Harada et al., "Ferulic acid induces neural progenitor cell proliferation *in vitro* and *in vivo*," *Neuroscience*, vol. 165, no. 2, pp. 515–524, 2010.

[135] L. Zhang, Y. Fang, Y. Xu et al., "Curcumin improves amyloid $\beta$-peptide (1-42) induced spatial memory deficits through BDNF-ERK signaling pathway," *PLoS One*, vol. 10, no. 6, p. e0131525, 2015.

[136] G. Y. Su, J. Y. Yang, F. Wang et al., "Antidepressant-like effects of Xiaochaihutang in a rat model of chronic unpredictable mild stress," *Journal of Ethnopharmacology*, vol. 152, no. 1, pp. 217–226, 2014.

[137] S. de Nicoló, L. Tarani, M. Ceccanti et al., "Effects of olive polyphenols administration on nerve growth factor and brain- derived neurotrophic factor in the mouse brain," *Nutrition*, vol. 29, no. 4, pp. 681–687, 2013.

[138] H. Yu, K. Ohhashi, T. Tanaka et al., "*Rehmannia glutinosa* induces glial cell line-derived neurotrophic factor gene expression in astroglial cells via cPKC and ERK1/2 pathways independently," *Pharmacological Research*, vol. 54, no. 1, pp. 39–45, 2006.

[139] M. Naoi, W. Maruyama, and M. Shamoto-Nagai, "Type A monoamine oxidase and serotonin are coordinately involved in depressive disorders: from neurotransmitter imbalance to impaired neurogenesis," *Journal of Neural Transmission*, vol. 125, no. 1, pp. 53–66, 2018.

[140] K. Inaba-Hasegawa, M. Shamoto-Nagai, W. Maruyama, and M. Naoi, "Type B and A monoamine oxidase and their inhibitors regulate the gene expression of Bcl-2 and neurotrophic factors in human glioblastoma U118MG cells: different signal pathways for neuroprotection by selegiline and rasagiline," *Journal of Neural Transmission*, vol. 124, no. 9, pp. 1055–1066, 2017.

[141] R. M. Bruno and L. Ghiadoni, "Polyphenols, antioxidants and the sympathetic nervous system," *Current Pharmaceutical Design*, vol. 24, no. 2, pp. 130–139, 2018.

[142] M. S. Uddin, M. T. Kabir, D. Tewari, B. Mathew, and L. Aleya, "Emerging signal regulating potential of small molecule biflavonoids to combat neuropathological insults of Alzheimer's disease," *Science of the Total Environment*, vol. 700, p. 134836, 2020.

[143] P. Wang, C. J. Jeng, C. L. Chien, and S. M. Wang, "Signaling mechanisms of daidzein-induced axonal outgrowth in hippocampal neurons," *Biochemical and Biophysical Research Communications*, vol. 366, no. 2, pp. 393–400, 2008.

[144] S. L. Hwang, J. A. Lin, P. H. Shih, C. T. Yeh, and G. C. Yen, "Pro-cellular survival and neuroprotection of citrus flavonoid: the actions of hesperetin in PC12 cells," *Food & Function*, vol. 3, no. 10, pp. 1082–1090, 2012.

[145] J. M. Russell, "Sodium-potassium-chloride cotransport," *Physiological Reviews*, vol. 80, no. 1, pp. 211–276, 2000.

[146] K. I. Nakajima, H. Miyazaki, N. Niisato, and Y. Marunaka, "Essential role of NKCC1 in NGF-induced neurite outgrowth," *Biochemical and Biophysical Research Communications*, vol. 359, no. 3, pp. 604–610, 2007.

[147] K. I. Nakajima, N. Niisato, and Y. Marunaka, "Quercetin stimulates NGF-induced neurite outgrowth in PC12 cells via activation of Na/K + /2Cl - cotransporter," *Cellular Physiology and Biochemistry*, vol. 28, no. 1, pp. 147–156, 2011.

[148] M. J. Diógenes, C. C. Fernandes, A. M. Sebastião, and J. A. Ribeiro, "Activation of adenosine A2A receptor facilitates brain-derived neurotrophic factor modulation of synaptic transmission in hippocampal slices," *The Journal of Neuroscience*, vol. 24, no. 12, pp. 2905–2913, 2004.

[149] M. T. Tebano, A. Martire, R. L. Potenza et al., "Adenosine A2Areceptors are required for normal BDNF levels and BDNF-induced potentiation of synaptic transmission in the mouse hippocampus," *Journal of Neurochemistry*, vol. 104, pp. 279–286, 2007.

[150] S. Wiese, S. Jablonka, B. Holtmann et al., "Adenosine receptor A2A-R contributes to motoneuron survival by transactivating the tyrosine kinase receptor TrkB," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 43, pp. 17210–17215, 2007.

[151] H. C. Cheng, H. M. Shih, and Y. Chern, "Essential Role of cAMP-response Element-binding Protein Activation by $A_{2A}$ Adenosine Receptors in Rescuing the Nerve Growth Factor-induced Neurite Outgrowth Impaired by Blockage of the MAPK Cascade," *The Journal of Biological Chemistry*, vol. 277, no. 37, pp. 33930–33942, 2002.

[152] M. Flajolet, Z. Wang, M. Futter et al., "FGF acts as a cotransmitter through adenosine $A_{2A}$ receptor to regulate synaptic plasticity," *Nature Neuroscience*, vol. 11, no. 12, pp. 1402–1409, 2008.

[153] S. J. Jeon, H. Bak, J. Seo et al., "Oroxylin a induces BDNF expression on cortical neurons through adenosine A2Areceptor stimulation: a possible role in neuroprotection," *Biomolecules & Therapeutics*, vol. 20, no. 1, pp. 27–35, 2012.

[154] Z. Zhang, L. Cai, X. Zhou et al., "Methyl 3,4-dihydroxybenzoate promote rat cortical neurons survival and neurite outgrowth through the adenosine A2a receptor/PI3K/Akt signaling pathway," *Neuroreport*, vol. 26, no. 6, pp. 367–373, 2015.

[155] M. S. Uddin, M. M. Rahman, M. Jakaria et al., "Estrogen signaling in Alzheimer's disease: molecular insights and therapeutic targets for Alzheimer's dementia," *Molecular Neurobiology*, vol. 57, no. 6, pp. 2654–2670, 2020.

[156] M. S. Uddin, M. T. Kabir, M. S. Rahman et al., "Revisiting the amyloid cascade hypothesis: from Anti-A$\beta$ therapeutics to auspicious new ways for Alzheimer's disease," *International Journal of Molecular Sciences*, vol. 21, no. 16, p. 5858, 2020.

[157] Z. Wang, X. Zhang, H. Wang, L. Qi, and Y. Lou, "Neuroprotective effects of icaritin against beta amyloid-induced neurotoxicity in primary cultured rat neuronal cells via estrogen-dependent pathway," *Neuroscience*, vol. 145, no. 3, pp. 911–922, 2007.

[158] H. Ushikubo, S. Watanabe, Y. Tanimoto et al., "3,3′,4′,5,5′ -Pentahydroxyflavone is a potent inhibitor of amyloid $\beta$ fibril formation," *Neuroscience Letters*, vol. 513, no. 1, pp. 51–56, 2012.

[159] S. Y. Hong, W. S. Jeong, and M. Jun, "Protective effects of the key compounds isolated from Corni fructus against $\beta$-amyloid-induced neurotoxicity in pc12 cells," *Molecules*, vol. 17, no. 9, pp. 10831–10845, 2012.

[160] H. J. Heo and C. Y. Lee, "Epicatechin and catechin in cocoa inhibit amyloid $\beta$ protein induced apoptosis," *Journal of Agricultural and Food Chemistry*, vol. 53, no. 5, pp. 1445–1448, 2005.

[161] Y. Yang, G. X. Bian, and Q. J. Lu, "Neuroprotection and neurotrophism effects of liquiritin on primary cultured hippocampal cells," *Zhongguo Zhongyao Zazhi*, vol. 33, no. 8, pp. 931–935, 2008.

[162] P. Meng, H. Yoshida, K. Tanji et al., "Carnosic acid attenuates apoptosis induced by amyloid-$\beta$ 1-42 or 1-43 in SH- SY5Y human neuroblastoma cells," *Neuroscience Research*, vol. 94, pp. 1–9, 2015.

[163] X. Mu, G. He, Y. Cheng, X. Li, B. Xu, and G. Du, "Baicalein exerts neuroprotective effects in 6-hydroxydopamine-induced experimental parkinsonism in vivo and in vitro," *Pharmacology, Biochemistry, and Behavior*, vol. 92, no. 4, pp. 642–648, 2009.

[164] T. Silva, J. Bravo, T. Summavielle et al., "Biology-oriented development of novel lipophilic antioxidants with neuroprotective activity," *RSC Advances*, vol. 5, no. 21, pp. 15800–15811, 2015.

[165] M. Tavakkoli, R. Miri, A. R. Jassbi et al., "Carthamus, Salvia and Stachys species protect neuronal cells against oxidative stress-induced apoptosis," *Pharmaceutical Biology*, vol. 52, no. 12, pp. 1550–1557, 2014.

[166] V. K. Gupta, Y. You, J. C. Li, A. Klistorner, and S. L. Graham, "Protective effects of 7,8-dihydroxyflavone on retinal ganglion and rgc-5 cells against excitotoxic and oxidative stress," *Journal of Molecular Neuroscience*, vol. 49, no. 1, pp. 96–104, 2013.

[167] J. Garrido, A. Gaspar, E. M. Garrido et al., "Alkyl esters of hydroxycinnamic acids with improved antioxidant activity and lipophilicity protect PC12 cells against oxidative stress," *Biochimie*, vol. 94, no. 4, pp. 961–967, 2012.

[168] M. Sajad, J. Zargan, M. A. Zargar et al., "Quercetin prevents protein nitration and glycolytic block of proliferation in hydrogen peroxide insulted cultured neuronal precursor cells (NPCs): implications on CNS regeneration," *Neurotoxicology*, vol. 36, pp. 24–33, 2013.

[169] J. Chen, K. W. Chua, C. C. Chua et al., "Antioxidant activity of 7,8-dihydroxyflavone provides neuroprotection against glutamate-induced toxicity," *Neuroscience Letters*, vol. 499, no. 3, pp. 181–185, 2011.

[170] N. A. G. dos Santos, N. M. Martins, R. . B. Silva, R. S. Ferreira, F. M. Sisti, and A. C. . Santos, "Caffeic acid phenethyl ester (CAPE) protects PC12 cells from $MPP^+$ toxicity by inducing

the expression of neuron- typical proteins," *Neurotoxicology*, vol. 45, pp. 131–138, 2014.

[171] B. Liu, H. Zhang, C. Xu et al., "Neuroprotective effects of icariin on corticosterone-induced apoptosis in primary cultured rat hippocampal neurons," *Brain Research*, vol. 1375, pp. 59–67, 2011.

[172] S. B. Oh, H. R. Park, Y. J. Jang, S. Y. Choi, T. G. Son, and J. Lee, "Baicalein attenuates impaired hippocampal neurogenesis and the neurocognitive deficits induced by $\gamma$-ray radiation," *British Journal of Pharmacology*, vol. 168, no. 2, pp. 421–431, 2013.

[173] R. Liu, M. Gao, G. F. Qiang et al., "The anti-amnesic effects of luteolin against amyloid $\beta_{25\text{-}35}$ peptide-induced toxicity in mice involve the protection of neurovascular unit," *Neuroscience*, vol. 162, no. 4, pp. 1232–1243, 2009.