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Regulation of Neural Stem Cell Fate by Natural Products

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Abstract

Neural stem cells (NSCs) can proliferate and differentiate into multiple cell types that constitute the nervous system. NSCs can be derived from developing fetuses, embryonic stem cells, or induced pluripotent stem cells. NSCs provide a good platform to screen drugs for neurodegenerative diseases and also have potential applications in regenerative medicine. Natural products have long been used as compounds to develop new drugs. In this review, natural products that control NSC fate and induce their differentiation into neurons or glia are discussed. These phytochemicals enable promising advances to be made in the treatment of neurodegenerative diseases.

Key Words: Neural stem cells, Cell fate, Neurogenesis, Differentiation, Antioxidative, Neuroprotection

INTRODUCTION

Stem cells (SCs) can self-renew and differentiate into various cell types (Kim, 2011). Embryonic stem cells (ESCs) are derived from the inner cell mass of the blastocyst and because they can be differentiated into all types of cells that the body is composed of, they are referred to as pluripotent (Thomson *et al*., 1998). Neural stem cells (NSCs) or neural progenitor cells (NPCs) can proliferate but can only differentiate into neural cells such as neurons, astrocytes, and oligodendrocytes, and are therefore categorized as multipotent (Gage, 2000). The identification of SCs has led to promising advances in the treatment of diseases since these cells have the potential to replace damaged cells after differentiation into the appropriate cell types. However, more research is required to overcome immune rejection after transplantation and to be able to safely and successfully transplant ectopically managed cells into the body before ESCs or induced pluripotent stem cells (IPSCs) can be used for regenerative medicine. SCs, especially human SCs, provide an efficient platform for the development of new drugs because they can be used to evaluate the efficacy and toxicity of drug candidates (Kim and Jin, 2012). Controlling SC fate by chemicals and natural products has potential applications in therapeutic use. Natural products are chemical compounds or substances endogenously produced by living organisms such as plants and animals. Natural products have been important sources for developing medicinal treatments. Traditionally, plant extracts were used in Asian countries to treat injuries or diseases (referred as traditional medicine) and have recently attracted attention for their potential to be developed into novel drugs (Harvey *et al*., 2015). Not only can normal cells that are lost in patients suffering from diseases be regenerated, but limitations of cell-based regenerative medicine can also be overcome by facilitating the production of neurons or glia from endogenous NSCs in the brain. Thus, molecules that control endogenous SCs or NSCs can be used as pharmacological agents to treat neurodegenerative diseases. Phytochemicals have recently been recognized as alternatives for treating neurodegenerative diseases such as Alzheimer's disease (AD) (Shal *et al*., 2018). They are known to have anti-oxidative and anti-inflammatory effects and to increase cell survival (Dar *et al*., 2016; Kornberg *et al*., 2018; Safaeinejad *et al*., 2018). Moreover, some natural products have been reported to control NSC fate (Liu *et al*., 2007; Dong *et al*., 2012; Kim and Jin, 2012; Kong *et al*., 2015). This review focuses on recent evidence that NSC fate can be regulated by natural products.

NSCS/NPCS FOR NEURODEGENERATIVE DISEASES

Neurodegenerative diseases including Parkinson's disease (PD), AD, and Huntington's disease (HD) are caused by neuronal loss and subsequent brain malfunction (MacDonald *et al*., 1993; Kim, 2011). For example, in PD, dopaminergic (DA) neurons, whose cell bodies are located in the substantia nigra

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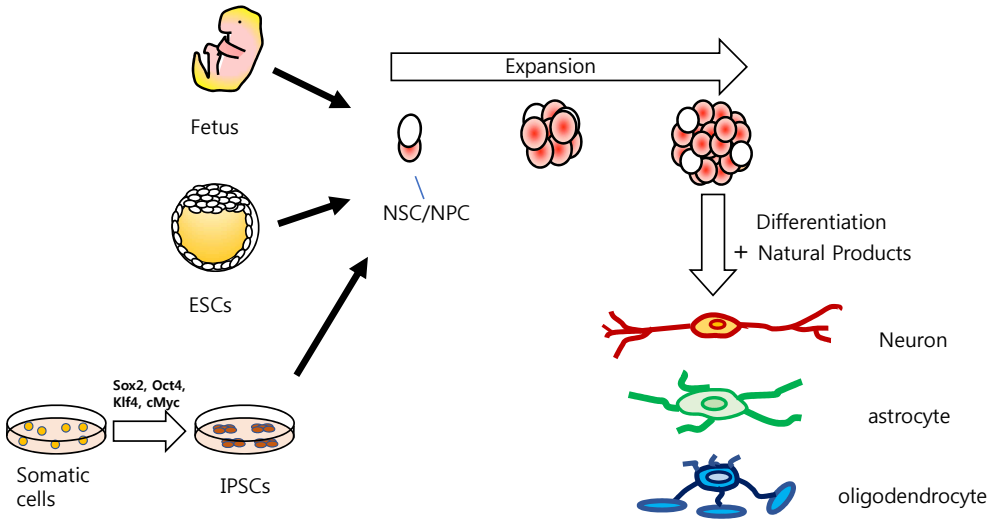

Fig. 1. Schematic illustration of cells that can produce neurons and glia. Neural stem cells (NSCs) or neural progenitor cells (NPCs) can be derived from the fetus, embryonic stem cells (ESCs), and induced pluripotent stem cells (IPSCS). NSCs/NPCs proliferate in the presence of mitogens and can differentiate into neurons, astrocytes, or oligodendrocytes with the appropriate stimuli and/or in the presence of natural products.

and project into the striatum, are lost (Kim, 2011). Because DA neurons control movement, patients with PD suffer from bradykinesia, rigidity, and depression. AD is a neurodegenerative disease that results in the loss of memory, which leads to dementia due to the loss of neurons in the basal forebrain, hippocampus, and cortex (Monroy *et al*., 2013). HD is caused by a mutated *HTT* gene that has expanded CAG repeats, which encode poly-glutamine stretches resulting in a dopamine imbalance in the striatum (MacDonald *et al*., 1993). Patients with HD show abnormal dance-like movements and progressive breakdown of nerve cells in the brain (Chen *et al*., 2013). Mainly striatal and cortical neurons are lost in HD (Chen *et al*., 2013). Studies to recover or replace neurons have been extensively pursued and the discovery of SCs that can be manipulated to produce cells of interest has led to promising advances for novel therapies.

A study performed in 1965 reported that many granule cells of the dentate gyrus (DG) are newly generated as determined by thymidine-H^3 injection in young rats (Altman and Das, 1965). In the human DG, neurogenesis was also confirmed to occur in adults (Eriksson *et al*., 1998; Goncalves *et al*., 2016). These findings provide evidence that in some areas of the adult brain, including the subventricular zone of the hippocampal DG, new neurons can be generated by controlling residing endogenous NSCs with suitable stimuli. The identification of cells or NSCs that can generate neurons in the adult brain initiated studies to discover drugs that can modulate NSC fate into specific neurons or glia (Kong *et al*., 2015; Shin *et al*., 2015; Lee *et al*., 2016). With advances in NSC culture from developing animals, human ESCs, or IPSCs, NSCs have been used to generate lost neurons to treat neurodegenerative diseases or study mechanisms of neuro-degeneration or neuro-regeneration (Fig. 1) (Reynolds *et al*., 1992; Reynolds and Weiss, 1992; Schneider *et al*., 2007; Akhtar *et al*., 2018). However, protocols that are currently used for the derivation of NSCs or neurons from ESCs or IPSCs still produce other types of cells and have the possibility of forming teratomas (Cieslar-Pobuda *et al*., 2017). Thus, the protocols need to be optimized before they can be applied in regenerative medicine. Recently, in addition to soluble factors that are required for proper cell development, culture dish surfaces and microfluidic chambers that are effective in generating gradients of soluble factors have also been studied to identify the optimal environment for SC culture and differentiation (Cha *et al*., 2017; Kim *et al*., 2018).

NSCs derived from the fetus only generate neural cells and do not form teratomas. These cells are more committed than ESCs and are restricted to production of desired neurons. However, fetus-derived NSCs are still useful for studying the development of the nervous system and for drug screening and regenerative medicine (Kong *et al*., 2015; Shin *et al*., 2015; Lee *et al*., 2016; Kong *et al*., 2018). NSCs derived from developing fetuses demonstrate an *in vivo* developmental sequence in that they produce neurons first, then astrocytes, followed by oligodendrocytes. Although they are restricted, NSCs can be induced to generate neurons and glia by chemicals or growth factors (Sauvageot and Stiles, 2002). In addition, depending on the brain region from which they are derived, NSCs show specific characteristics (Kim *et al*., 2009). Animal brain sizes have increased throughout evolution, and different regions of the brain develop at specific rates (Bradbury, 2005; Paredes *et al*., 2016). For example, the cortex expands faster and to a greater extent than other areas of the brain and neurons generated from the midbrain are on average longer than those generated from the cortex. Interestingly, these characteristics are recapitulated in NSCs/NPCs derived from different regions such as the cortex and midbrain (Kim *et al*., 2009). Human NSCs/NPCs derived from the developing cortex are highly proliferative and produce large numbers of neurons, whereas NSCs from the midbrain divide slowly and produce fewer neurons (Kim *et al*., 2009). The specific regional characteristics are retained when ectopic genes are introduced. For

Table 1. Natural products that regulate NSC fate

Name	Plant origin	Effects in NSCs	Refs
Asarone	*Rhizoma Acori tatarinowii*	Increases NSC proliferation and induces neurogenesis	Mao *et al*., 2015
Bryostatin-1	*Bugula neritina*	Increases neurogenesis Promotes differentiation of oligodendrocyte progenitor cells Reduces inflammation	Safaeinejad *et al*., 2018
Casticin	*Croton betulaster*	Increases neurogenesis and oligodendrocytogenesis Exerts anti-cancer effect Exerts anti-inflammatory effect	de Sampaio e Spohr *et al*., 2010; Chou *et al*., 2018; Liou *et al*., 2018
Curcumin	*Curcuma longa*	Increases neurogenesis Increases proliferation of NSCs Detects amyloid-β	Garcia-Alloza *et al*., 2007; Kim *et al*., 2008; Liao *et al*., 2012; Tiwari *et al*., 2014, 2016; Wang *et al*., 2017; Chen *et al*., 2018b;
Garcinol	*Garcinia indica*	Induces neurogenesis Induces cancer cell death	Weng *et al*., 2011; Zhou *et al*., 2017; Huang *et al*., 2018
Ginkgo biloba extract	*Ginkgo biloba*	Provides neuroprotection Improves cardiovascular activity and cognitive function Increases neurogenesis	Tchantchou *et al*., 2007; Wang and Han, 2015; Osman *et al*., 2016; Tian *et al*., 2017; Yuan *et al*., 2017
Ginsenoside Rg1	*Panax notoginseng*	Increases neurogenesis in adipose-derived SCs through miRNA-124 Improves cognitive function Exerts anti-depressant effects Increases neurogenesis	Jiang *et al*., 2012; Wu *et al*., 2013; Dong *et al*., 2017; Chen *et al*., 2018a
Ginsenoside Rg5	*Panax notoginseng*	Increases neurogenesis and decreases astrocytogenesis Ca^{2+} channel blocker inhibits the neurogenesis of Rg5	Liu *et al*., 2007
Kuwanon V	*Morus bombycis*	Increases neurogenesis Blocks proliferation Overcomes proliferation signal induced by mitogens Increases cell survival	Kong *et al*., 2015
Nelumbo nucifera rhizome extract	*Nelumbo nucifera*	Increases NSCs and immature neurons	Yang *et al*., 2008; Yoo *et al*., 2011
NeuroAiD		Increases neurogenesis and cell proliferation	Heurteaux *et al*., 2010; Chan and Stanton, 2016
Phloroglucinol	*Hypericum longistylum*	Induces differentiation of NSCs, particularly into serotonergic neurons	Wang *et al*., 2018
Salvia miltiorrhiza	*Salvia miltiorrhiza*	Increases NSCs and induce neurogenesis Facilitates functional recovery in ischemic model	Shu *et al*., 2014
Tenuigenin	*Polygala tenuifolia*	Promotes NSC proliferation and increases neurogenesis Exerts anti-inflammatory effect	Chen *et al*., 2012; Yuan *et al*., 2012; Fan *et al*., 2017
Walnut oil	*Juglans regia*	Induces mesenchymal stem cell line differentiation into neurons	Singh and Sherpa, 2017

example, transduction of *ASCL1* can generate neurons from NSCs derived from the midbrain, and these *ASCL1*-generated neurons from the midbrain were bigger and had more neurites than those derived from NSCs in the cortex (Kim *et al*., 2009).

Although fewer neurons are generated, modulating endogenous NSC fate using chemicals or natural products can

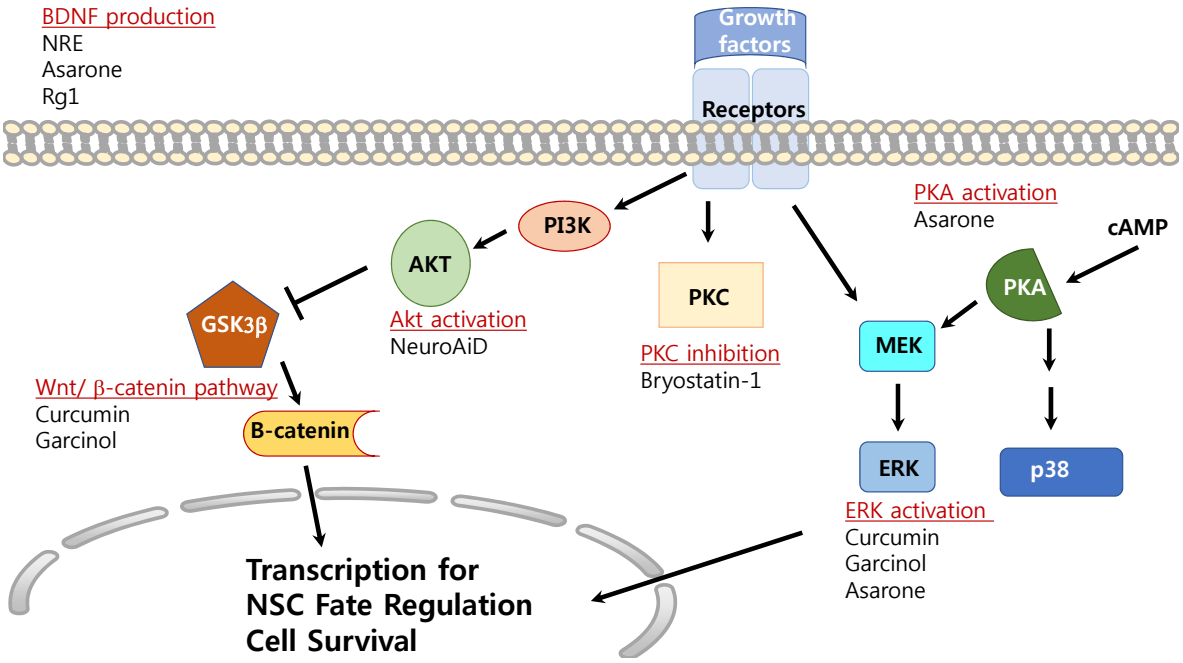

Fig. 2. Possible signal transduction mechanisms of natural products for induction of neurogenesis other than anti-oxidative effects and anti-inflammatory effects. Extracellular signal-regulated kinases (ERKs), Protein kinase A (PKA), Akt, WNT/β-catenin, PKC and brain-derived neurotrophic factor (BDNF) pathways/signals are involved in the neuroprotection and neurogenesis of natural products listed in this review.

be another strategy for treating neurodegenerative diseases. Human NSCs are a good source of cells to screen and identify new drugs. However, it is difficult to obtain enough human NSCs from aborted fetal tissue. NSCs from other species, ESCs, or IPSCs have also been used successfully as platforms for drug screening (Bahmad *et al*., 2017). Identification and culture of mouse ESCs began in the early 1980s and human ESC culture was first introduced by Thomson and colleagues in the late 1990s (Evans and Kaufman, 1981; Martin, 1981; Thomson *et al*., 1998). Since then, much effort has been dedicated to identify the conditions for generating specific functional types of neurons, such as DA neurons and motor neurons (Cooper *et al*., 2010; Du *et al*., 2015). However, because of the disadvantages of human ESCs for regenerative medicine such as immune rejection, approaches to overcome their limitations have been investigated. By introducing ESC-specific genes, such as those encoding SOX2, cMYC, OCT3/4, and KLF4, somatic cells can be converted into cells that possess ESC features, which are referred to as IPSCs (Takahashi and Yamanaka, 2006). This breakthrough study revolutionized research to identify the detailed mechanisms of neurodegenerative diseases because disease cell models could be established and studied by generating IPSCs using somatic cells from patients (Sances *et al*., 2016). For example, disease-specific IPSCs from patients with PD, HD, amyotrophic lateral sclerosis, and spinal muscular atrophy (SMA) have been generated successfully (Ebert *et al*., 2009; Alves *et al*., 2015; Kikuchi *et al*., 2017; Vigont *et al*., 2018). IPSCs generated from individuals with SMA differentiated into motor neurons and astrocytes normally at early time points, but motor neurons were not generated and did not survive efficiently at later time points in the experiments, which recapitulates the disease status (Ebert *et al*., 2009). This confirms the concept that IPSCs can be used as a model to screen drug candidates.

Neurodegenerative diseases are caused by neuronal damage or loss. Thus, it is important to identify mechanisms through which NSCs differentiate into neurons, astrocytes, and oligodendrocytes. The development of drugs that can regulate NSC fate and facilitate the generation of neurons or glia that aid the proper function of neurons is important for therapeutic applications.

NATURAL PRODUCTS THAT MODULATE NSC FATE

Natural products are important sources for developing therapeutic medicines. The contribution of natural products to new drug discovery should not be overlooked. For example, the first statin to be used to reduce cholesterol in blood by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase was developed from *Penicillium citrinum* (Endo *et al*., 1976). In addition, the widely-used aspirin is a synthetic molecule modified from salicin, an active ingredient in willow bark, and has long been used to reduce fever, inflammation, and clot formation.

Differentiation of NSCs into neurons occurs only during early development, and many synthetic chemical compounds and natural products are known to control NSC fate (Kim and Jin, 2012; Yoon *et al*., 2013; Kong *et al*., 2015; Lee *et al*., 2016). Natural products may have advantages over synthetic compounds because they may possess an innate stereochemistry that allows them to fit into the protein binding pockets and serve as substrates (Harvey *et al*., 2015). Because natural products are generated from living organisms, they may have additional biological benefits (Harvey *et al*., 2015). This review focuses on natural products that regulate NSC fate (Table 1,

Fig. 2).

Asarone, an active component of *Rhizoma Acori tatarinowii*, is reported to enhance the proliferation of mouse hippocampal NSCs and to promote neurogenesis (Mao *et al*., 2015). Extracellular signal-regulated kinase (ERK) activation appears to be critical for its ability to induce neurogenesis and proliferation (Mao *et al*., 2015). When α-asarone or β-asarone was administered to PC12 cells with nerve growth factor, elongated neurites were generated through protein kinase A and cAMP-responsive element binding protein activation (Lam *et al*., 2016). In addition, β-asarone has been reported to increase the expression of brain-derived neurotrophic factor (BDNF), enhance neurogenesis in the hippocampus and recover behavioral functions determined by forced swim and sucrose preference tests in a chronic unpredictable mild stress rat model (Dong *et al*., 2014).

Bryostatin, a macrolide and natural marine product, is considered to be a neuroprotective agent since it attenuates neuronal death in ischemic brain induced by middle cerebral artery occlusion (MCAO), decreases inflammation, and enhances cognitive function (Tan *et al*., 2013). Bryostatin-1 is known to have anti-oxidant properties, decreases matrix metalloproteinase (MMP) 1, 3, 9, 11 activity, activates protein kinase C (PKC) with short-term exposure, inhibits PKC with long-term exposure, and promotes neurogenesis and differentiation of oligodendrocyte progenitor cells (Kortmansky and Schwartz, 2003; Sun *et al*., 2008; Safaeinejad *et al*., 2018). Bryostatin-1 suppresses inflammation by inhibiting inflammation related signals mediated by Th1, one of the various types of T helper cells and by activating Th2, another T helper cell type, that is known to have anti-inflammatory effects both *in vitro* (bone marrow-derived dendritic cells) and *in vivo* (adult mice, 6-8 weeks of age) by acting as a Toll-like receptor 4 ligand (Ariza *et al*., 2011). In mice with experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (MS), Bryostatin-1 cured and prevented neurological defect and reduced inflammation in immune cells (Kornberg *et al*., 2018). It has been known that MMPs loosen the blood brain barrier and allow increased penetration of inflammatory cells into the CNS (Safaeinejad *et al*., 2018). MMPs are also reported to increase demyelination in the CNS (Safaeinejad *et al*., 2018). Co-administration of intravenous Bryostiatin-1 infusion with oral α-tocopherol improved water maze tasks in adult male rats and Bryostatin-1 increased neurogenesis by increasing cell survival and enhanced BDNF activity when administered after cerebral ischemia in rats (Sun and Alkon, 2008; Sun *et al*., 2008). In the process of screening oligodendrocyte-inducing drugs among PKC inhibitors, Bryostatin-1 promoted oligodendrocyte progenitor cells in the presence of myelin protein extracts which are known to be an inhibitory myelin substrate (Gonzalez *et al*., 2016). Thus, the decreased activity of MMPs by Brytostatin-1 appears to reduce the spread of inflammation and demyelination in the CNS and provides effective therapeutic effects on MS (Kornberg *et al*., 2018; Safaeinejad *et al*., 2018).

Casticin, a flavonoid component of *Croton betulaster*, increases neurogenesis through neuroprotection without affecting astrocyte and oligodendrocyte populations in rat cortical NPCs (de Sampaio e Spohr *et al*., 2010). Intriguingly, soluble factors appear to be involved in the neuroprotection-mediated neuronal increase because the neuronal population increased when NPCs were cultured with casticin-treated astrocytes or treated with conditioned media from casticin-treated astrocytes (de Sampaio e Spohr *et al*., 2010). Additionally, casticin is known to have anti-cancer activity and can induce DNA damage, apoptosis, and G2/M phase arrest (Chou *et al*., 2018). The anti-inflammatory effects of casticin enable its use in treating asthma: in ovalbumin-induced asthma models of female mice, casticin decreased airway sensitivity and oxidative responses in the lungs (Liou *et al*., 2018).

Curcumin is a phenolic component from *Curcuma longa* that has been widely consumed worldwide as a spice (Esatbeyoglu *et al*., 2012). Curcumin exerts an anti-depressant effect by protecting neurons and promoting hippocampal neurogenesis in chronically stressed rats (Xu *et al*., 2007). Moreover, curcumin prevents stress-induced reductions of 5-HT_{1A} and BDNF expression (Xu *et al*., 2007). When aged rats were fed curcumin in the diet for 6 and 12 weeks, DG cell proliferation was enhanced and memory was improved (Dong *et al*., 2012). Interestingly, curcumin increased the growth of neurites by activating ERKs and protein kinase C in PC12 cells (Liao *et al*., 2012). It is suggested that curcumin induces neurogenesis via the WNT/β-catenin pathway and increases GSK-3β in bisphenol A-treated rats or celecoxib-treated NPCs or neurons (Tiwari *et al*., 2016; Wang *et al*., 2017). In addition, the Notch intracellular domain level increased in MCAO ischemic rats treated with curcumin compared to that in vehicle-treated animals (Liu *et al*., 2016). Curcumin can also be applied as a diagnostic and/or therapeutic material to detect and disaggregate amyloid-β proteins because it crosses the blood-brain barrier, possesses natural fluorescence, has high affinity for senile plaques, and even clears or reduces the plaques (Garcia-Alloza *et al*., 2007; Chen *et al*., 2018b). When curcumin was administered in the form of curcumin-loaded nanoparticles, it induced neurogenesis and NSC proliferation through the WNT/β-catenin pathway in adult rat hippocampus and in cultured NSCs (Tiwari *et al*., 2014). Inhibiting the WNT pathway using siRNAs or pharmacological blockers reduced curcumin-mediated neurogenesis (Tiwari *et al*., 2014). Curcumin exhibited concentration-dependent effects in that low concentrations of curcumin stimulated mouse NSC proliferation through ERK and p38 kinases, whereas high concentrations caused cell death (Kim *et al*., 2008).

Garcinol, found in *Garcinia indica* fruit rind, activates ERK for up to 20 hours, induces neurogenesis, and promotes neurite outgrowth in cortical NPCs (Weng *et al*., 2011). Garcinol is also known to induce cancer cell death via down-regulating/inactivating the WNT/β-catenin signaling pathway and inactivating signal transducer and activator of transcription 3 (Zhou *et al*., 2017; Huang *et al*., 2018).

Ginkgo biloba extract (GBE) has been used as traditional medicine in China and is known to improve cardiovascular activity and cognitive functions including memory, learning, and attention (Tian *et al*., 2017; Yuan *et al*., 2017). GBE has neuroprotective effects against amyloid-β- and hypoxia-induced neurotoxicity (Tchantchou *et al*., 2007). When tested in aged mice (two years old), GBE increased NSC proliferation and the production of doublecortin-positive neurons in the DG (Osman *et al*., 2016). When NSCs derived from mouse cochlea were treated with GBE, cell survival and neurogenesis were promoted with elongated neurite outgrowth (Wang and Han, 2015), suggesting that GBE may be beneficial for treating hearing loss.

The ginsenoside Rg1 is also known to promote neurogene-

sis in mouse adipose-derived SCs through miRNA-124 (Dong *et al*., 2017). When injected in rats along with D-galactose, Rg1 improved the cognitive deficit caused by D-galactose by reducing NSC senescence and oxidative stress (Chen *et al*., 2018a). Interestingly, Rg1 decreased the phosphorylation levels of protein kinase B and the mechanistic target of rapamycin (Chen *et al*., 2018a). In mouse models of depression, Rg1 showed anti-depressant-like effects through activating the BDNF signaling pathway and reducing corticosterone serum levels (Jiang *et al*., 2012). Rg1 reversed dendritic spine density and hippocampal neurogenesis in chronic mild stress mouse models of depression (Jiang *et al*., 2012). When treated in embryonic bodies, Rg1 induced neuron-like cells and neuron markers including neurofilament and β-tubulin III (Wu *et al*., 2013).

The panaxadiol glycosides Rg5, Rk1, and Rg3 were found to induce neurogenesis in epithermal growth factor-responsive NSCs (Liu *et al*., 2007). Rg5-induced neurogenesis at the expense of astrogliogenesis and neurogenesis was blocked when the Ca^{2+} channel antagonist nifedipine was used.

Kuwanon V (KWV), a phenolic compound found in the roots of the mulberry tree (*Morus bombycis*), is known to increase neurogenesis in rat NSCs (Kong *et al*., 2015). Interestingly, the neurogenic effect of KWV is strong enough to overcome the proliferation signals induced by growth factors; KWV induces neurogenesis not only during differentiation, but also during proliferation of NSCs (Kong *et al*., 2015). KWV inhibited NSC proliferation but did not affect astrocytogenesis (Kong *et al*., 2015). Although the detailed effects on the regulation of NSC fate are not known, the components isolated from the root of *Morus* species including cyclomulberrin, sanggenon I, morusin, KWU, KWE, moracin P, moracin O, and mulberrofuran Q, have been reported to increase survival of neurons (Lee *et al*., 2011, 2012). Interestingly, moracenin D from *Mori Cortex Radicis* induced *NURR1* expression but repressed α-synuclein mRNA expression and resulted in the protection of SH-SY5Y cells with a high dopamine concentration, suggesting that natural products in the *Morus* species are effective in regulating neural activity and survival (Ham *et al*., 2012).

Nelumbo nucifera rhizome extract (NRE) increased cell proliferation and doublecortin (an immature neuronal marker)-positive cell number in rats with scopolamine-induced amnesia (Yoo *et al*., 2011). In addition, NRE reinstated the decreased BDNF levels caused by scopolamine (Yoo *et al*., 2011). Moreover, NRE significantly increased memory function determined by a step-through passive avoidance test and neurogenesis through activating NSC proliferation and differentiation in rat DG (Yang *et al*., 2008).

NeuroAiD (MLC601 or MLC901) is a mixture of plant and animal derivatives and is used as traditional medicine in China to treat patients with strokes because it improves survival and behavioral function after ischemia (Heurteaux *et al*., 2010). MLC601 is a mixture of 9 plant components (radix astragali, radix salviae mitorrhizae, radix paeoniae rubrae, rhizoma chuan-xiong, radix angelicae sinensis, *Carthamus tinctorius*, *Prunus persica*, radix polygalae and rhizoma acori tata-rinowii) and 5 animal components (including *Hirudo*, *Eupolyphaga* seu *Steleophaga*, calculus bovis artifactus, *Buthus martensii* and Cornu saigae tataricae) (Heurteaux *et al*., 2013). MLC901 is used in Europe and is a simplified version that contain 9 plant components (Heurteaux *et al*., 2013). In global ischemic model rats, MLC901 decreased cell death, increased the numbers of newly generated neurons, and improved behavioral function which are mediated by reduction of BAX expression and AKT activation (Quintard *et al*., 2011). NeuroAiD also increases neurogenesis, promotes cell proliferation, and induces neurite outgrowth in rodent and human cells (Heurteaux *et al*., 2010). In human NPCs, microarray experiments revealed genes regulated by MLC901 and identified FGF19, FGF3, and others as potential targets for neurogenesis (Chan and Stanton, 2016).

Phloroglucinol derivatives from *Hypericum longistylum* are known to facilitate the differentiation of NPCs derived from ESCs, while particularly increasing serotonergic neurogenesis (Wang *et al*., 2018). The components of *Hypericum longistylum* have been suggested to function as protein tyrosine phosphatase 1B inhibitors and have potential to treat type II diabetes (Cao *et al*., 2017). *Hypericum longistylum* has long been used to cure depression in China, which may be attributed to the effects of the phloroglucinol derivatives (Wang *et al*., 2018).

Salvia miltiorrhiza (derived from the plant *Salvia miltiorrhiza*), a type of Chinese medicine, is known to have antioxidative and anti-inflammatory activities and has been used to treat neurological diseases (Bonaccini *et al*., 2015). When IPSCs were treated with Salvia miltiorrhiza, the NSC marker NES expression was increased and neurogenesis was induced (Shu *et al*., 2014). After Salvia miltiorrhiza was administered into rats with MCAO ischemic brain tissue, the treated rats had more neurons and showed better functional recovery (Shu *et al*., 2014). Depsides and tanshiones, the component of Salvia miltiorrhiza, are also known to be effective in memory improvement and cell survival in animal models of cerebral ischemia and AD (Mei *et al*., 2009; Bonaccini *et al*., 2015).

Tenuigenin, a component of *Polygala tenuifolia*, is reported to possess anti-inflammatory activity and protects DA neurons, possibly by suppressing activation of the pyrin domain-containing 3 inflammasome (Yuan *et al*., 2012; Fan *et al*., 2017). When tenuigenin was treated in neurosphere cultures of hippocampal NSCs, it promoted NSC proliferation as determined by bromodeoxyuridine, a thymidine analogue that is inserted into DNA during replication, assay and differentiation into neurons and astrocytes (Chen *et al*., 2012).

Walnut (*Juglans regia* L.) oil induces the differentiation of C3H10T1/2 cells, a murine mesenchymal stem cell line, into neuron-like cells with long outgrowths of axon-like structures (Singh and Sherpa, 2017). Homolocarpum seed oil, which is known to contain high amounts of α-linolenic acid, β-sitosterol, and campesterol, resulted in increased neurosphere formation when administered to adult male BALB/c mice without affecting *in vitro* differentiation of the harvested NSCs (Hamedi *et al*., 2015).

The detailed mechanisms of how natural products induce NSC proliferation or differentiation are not yet known. Some studies revealed that phytochemicals alter signal transduction such as ERK activation or WNT/β-catenin signaling. Recent evidence suggests that these signals not only influence gene transcription, but also epigenetic modification and regulation of SC fate (Kim, 2011; Kong *et al*., 2018). For example, histone proteins have long been considered scaffold proteins that help to contain DNA within the limited space of the nucleus, but recently their active role in controlling transcription by regulating the accessibility of genes to transcription factors has been revealed (Kim and Rosenfeld, 2010; Kim, 2011; Rothbart and Strahl, 2014). It would be of great interest to find common mechanisms of neurogenesis induction by natural products, if

any exist, and apply them in a medicinal context to regenerate neurons that are lost in neurodegenerative diseases.

CONCLUSIONS

NSCs derived from embryos, ESCs, or IPSCs are good platforms to screen drugs that can increase neurogenesis or control NSC fate. Several phytochemicals have been reported to control NSC fate. Since specific types of neurons are lost in neurodegenerative diseases, phytochemicals that can regenerate neurons would be important for therapeutic applications. Although the detailed underlying mechanisms are not clearly known, natural products hold promise for the development of new drugs to treat neurodegenerative diseases.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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