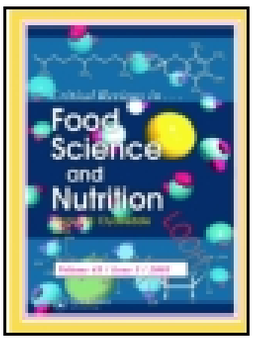

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Seyed Zachariah Moradi, Faramarz Jalili, Negin Farhadian, Tanuj Joshi, Mingfu Wang, Liang Zou, Hui Cao, Mohammad Hosein Farzaei & Jianbo Xiao (2021): Polyphenols and neurodegenerative diseases: focus on neuronal regeneration, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1865870

To link to this article: https://doi.org/10.1080/10408398.2020.1865870

Published online: 04 Jan 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1865870

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REVIEW

Polyphenols and neurodegenerative diseases: focus on neuronal regeneration

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ABSTRACT

Neurodegenerative diseases are questions that modern therapeutics can still not answer. Great milestones have been achieved regarding liver, heart, skin, kidney and other types of organ transplantations but the greatest drawback is the adequate supply of these organs. Furthermore, there are still a few options available in the treatment of neurodegenerative diseases. With great advances in medical science, many health problems faced by humans have been solved, and their quality of life is improving. Moreover, diseases that were incurable in the past have now been fully cured. Still, the area of regenerative medicine, especially concerning neuronal regeneration, is in its infancy. Presently allopathic drugs, surgical procedures, organ transplantation, stem cell therapy forms the core of regenerative therapy. However, many times, the currently used therapies cannot completely cure damaged organs and neurodegenerative diseases. The current review focuses on the concepts of regeneration, hurdles faced in the path of regenerative therapy, neurodegenerative diseases and the idea of using peptides, cytokines, tissue engineering, genetic engineering, advanced stem cell therapy, and polyphenolic phytochemicals to cure damaged tissues and neurodegenerative diseases.

KEYWORDS

Antioxidants; neurodegenerative diseases; neuronal regeneration; regenerative medicine; polyphenols

Regenerative medicine and its significant therapeutic potential

Tissue and organ shortage is an important public health issue, and the number of cases received transplantations is relatively small. Many ethical and conceptual aspects of organ transplantation are controversial because they are based on personal opinions as well as religious and geographical factors. Organ donation after brain death (a legal definition of death) is a major source for transplantation. Most of the organs get from live donations, especially from non-heart-beating donors. The main problem is the shortage of organ donors, and this is unlikely to be solved easily. Furthermore, transplantation is a very difficult procedure because there is a need for much of the medical character of the recipient to the donor in living donors or his family for a deceased donor. Immunological rejection of the donated body parts is an important problem in this field. Ethical issues must also be considered (Beyar 2011). Therefore, it seems that the availability of tissues and organ's supply is necessary. Laboratory-grown tissues, humanized animal organs and bioartificial organs may be some possible solutions. Regenerative medicine can help solve some of these problems (Dzobo et al. 2018). It is applicable for a variety of tissues, and organs, including skin, heart, kidney, liver and so on. Combinations of scaffolds, growth factors and stem cells are usually used in regenerative medicine for replacing the damaged tissue by acting as the original tissue or stimulating regeneration of the original tissue (Mao and Mooney 2015). So, the main problems of organ transplantation may potentially be solved through the use of regenerative medicine strategies.

Nervous system diseases and new therapeutic strategies

Nervous diseases are disorders that affect the central neuron system (CNS) or the peripheral neuron system (PNS) and can damage the brain, spinal cord, peripheral nerves, and neuromuscular function. Diseases of the nervous system fall into several categories. The most important vascular disorder is stroke and transient ischemic attack (TIA). Brain and spinal cord injury, peripheral neuropathy, brain, and spinal cord tumors are structural disorders of the brain.

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Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Multiple sclerosis (MS), and Alzheimer's disease (AD) are neurodegenerative disorders. The pathophysiology of neurodegenerative diseases is different, some of which impair memory and cognition and in some cases impair one's ability to move, breathe and speak (Abeliovich and Gitler 2016; Canter, Penney, and Tsai 2016; Taylor, Brown Jr and Cleveland 2016; Wyss-Coray 2016; Fakhri, Moradi, et al. 2020; Moradi et al. 2020). Treatments available for nervous system disorders include drug interventions, surgical procedures, physical/rehabilitation therapies, and pain management that are used alone or in combination. There is no cure for neurodegenerative diseases, and all treatments are aimed at reducing symptoms and maintaining the quality of life of the patient. Although thousands of new neurons are produced daily in the adult brain, its self-regeneration is very limited. Usually, physiological brain neurogenesis in mammals cannot compensate for severe brain damage. Essentially, current treatments focus on preventing neurodegenerative diseases and are unable to regenerate lost neurons. Supportive exogenous neurogenesis systems have been developed to treat nervous system diseases. Many biological compounds, including peptides, cytokines, genes, small molecules and growth factors along with stem cells have been investigated to improve brain injury rehabilitation (Forraz et al. 2013). Neurogenic effects of psychotropic drug's fluoxetine and paliperidone on neurogenesis of subventricular zone (SVZ) (Nasrallah, Hopkins, and Pixley 2010), characterization of the role of growth factors (EGF and VEGF), Noggin and brain-derived neurotrophic factors (BDNF) proteins in neural stem cell homeostasis (Lim et al. 2000) are examples of using these compounds to regenerate neurons. These molecules can be delivered directly or systemically to the brain parenchyma and have been shown to have a positive effect on stimulating endogenous neurogenesis. In situ production of these molecules by genetically modified cells can cause neural stem cells (NSCs) to proliferate (Hell et al. 2009; Sasaki et al. 2009; Kemp et al. 2010). Because of the ability of small molecules to mimic the activity of endogenous proteins and to regulate signaling pathways, these molecules are useful new tools in the treatment of brain injury (Longo et al. 2006). For example, lithium interacts with focal Wnt signaling to stimulate neurogenesis (Wada 2009). The remarkable role of miR-200 neuroprotection in cerebral ischemia has been demonstrated (Lee et al. 2010). The miR-200 is also a BMP signaling modulator that prevents neurogenesis (Samavarchi-Tehrani et al. 2010). The use of exogenous molecules in the treatment of CNS injuries has some problems because controlling their pharmacodynamic is difficult. Therefore, cell-based therapies have been developed to overcome the problems of these therapies. Exogenous cells support the regeneration process by secreting growth factors and cytokines, carry genes and provide sustained/controlled release of therapeutic molecules to damaged sites. Human stem cells, mainly stem cells extracted from the spinal cord or mesenchymal have been used systemically to treat nervous system diseases, including ischemic stroke, spinal cord injury, PD, MS, cerebral palsy and ALS. Brain stem cell transplantation is a valuable tool to replace and regenerate the CNS. The ability of anatomical reconstruction of the damaged brain is the main advantage of this treatment over simple drug therapies. The most important barrier to clinical translation of stem cell-based therapy is the lack of allogeneic sources and safe cell analogues that can differentiate functional neurons continuously and effectively in vivo. The problem of the direct delivery of stem cells to the nervous system is a lack of extracellular matrix-supporting proteins due to the necrotic/lancular nervous system. Thus, the rate of differentiation and viability of grafted cells is low and there are problems with the tracking. Additionally, the integration of cells with host tissues will be limited (Kozłowska et al. 2007). In general, the delivery of neuronal-committed stem cells has more beneficial effects than undifferentiated pluripotent stem cells. Furthermore, due to systemic delivery problems of large numbers of cells without control over the host site, intracranial delivery of an accurate number of neuroblasts appears to be more efficient. It should be noted that the reconstruction of large brain cavities like other organ regeneration techniques requires the use of implantable 3 D devices to be supported by scaffolds or extracellular matrix proteins. Nervous tissue engineering is a new method that will be used soon to treat the damaged nervous system. Artificial nerve tissue can be produced in the laboratory using progenitor or NSCs with polymeric scaffolds (Ma et al. 2004). This type of treatment is used for stroke and spinal cord injury. The survival rate of cells transplanted directly into damaged brain tissue is enhanced by combining tissue engineering and reconstruction medicine (Park, Teng, and Snyder 2002). The structure and physical properties of the designed scaffolds, especially the size of the cavities and their elasticity should be very similar to that of soft brain tissue (Delcroix et al. 2010; Jurga et al. 2011). These scaffolds must be able to integrate with host neurons and have adequate support for blood vessels and exogenous neuroblasts. Examples of the designed scaffolds for drug, cell and gene delivery to the CNS are discussed in the next sections.

Polyphenols and their suitable effects in neurodegenerative disorders

Medicinal plants have been consumed in the treatment of various human disorders. A variety of studies have been carried out on traditional medicine for the investigation of their active constituents and phytochemicals, particular biological effects associated with the specific phytochemicals and their mechanism of actions in vitro and in vivo. Based on the historical consumption of medicinal plants and their experimental uses in the treatment of diseases, they are known as a valuable and enriched source of lead compounds and drugs, mostly with minimum toxicity in the body. Recently, many studies have been in progress for the identification and characterization of phytochemicals from medicinal and even dietary plants with positive effects on the neural systems, their biological effects, and the mechanisms, signaling pathways and gene expressions involved in their therapeutic

Table 1. Classification of tannins and a neuroprotective compound in each class.

Class of tannins	Pseudo tannin	True tannins			
		Complex tannins	Condensed tannins	Hydrolyzable tannins	
				Ellagitannins	Gallotannins
Plant source	*Strychnosnux-vomica*	–	*Camellia sinensis*	*Punica granatum*	*Quercus infectoria*
Active compound (tannin)	Chlorogenic acid		Epigallocatechin-3-gallate	Punicalagin	Tannic acid
Reference	(Heitman and Ingram 2017)		(Singh, Mandal, and Khan 2016)	(Olajide et al. 2014)	(Braidy et al. 2017)

actions (Kim, Kim, and Yang 2014; Naoi et al. 2017; Naoi, Shamoto-Nagai, and Maruyama 2019). Most of the neuroprotective phytochemicals possess antioxidant and anti-inflammatory properties, and their neuroprotective mechanisms have been attributed to these properties (Kim, Lee, and Lee 2010; Moradi et al. 2020).

Polyphenols are known as the largest group of plant secondary metabolites and their structure varied from hydroxyl groups attached to the aromatic ring in the simple phenols to highly complex polymeric compounds in tannins and lignins. Polyphenols are widespread in plants, and they appear individually or in combination with other groups of phytochemicals.

Based on their structure, polyphenols are strong anti-inflammatory and antioxidant compounds and possess widespread contribution in the treatment of variant diseases. Several clinical trials on the role of polyphenols consumption on the different neurodegenerative disorders have been undertaken (Scott 2004; McMahan et al. 2006; Weir 2014; Chou et al. 2016). The most widely known antioxidant nutrients are derived from phytochemicals (plant-derived chemicals) which include polyphenols in the form of flavonoids.

Flavonoids are a major bioactive group of polyphenols with more than 6000 types. Flavonoids are characterized by a fifteen-carbon structure comprising two fused rings (A and C) attached to an aromatic ring (B) via a carbon-carbon bond (Khan et al. 2020). Flavonoids are classified to different subdivisions based on the variations in the ring C.

Daidzein and genistein (isoflavones) (Qian et al. 2012; Aras et al. 2015), Apigenin and Luteolin (flavones) (Patil et al. 2014), quercetin and kaempferol (flavonols) (Lagoa et al. 2009; Barreca et al. 2016), epigallocatechin-3-gallate (EGCG) (flavanol) (Singh, Mandal, and Khan 2016), cyanidin and delphinidin (anthocyanins) (Strathearn et al. 2014), naringenin and hesperetin (flavanones) (Cirmi et al. 2016; Heidary Moghaddam et al. 2020) are some of the most known flavonoids of medicinal and dietary plants with protective roles in various neurodegenerative diseases. Lycopene (carotenoid) (Prema et al. 2015), curcumin (Hu et al. 2015; Fakhri, Pesce, et al. 2020), catalpol (iridoid glycoside) (Jiang et al. 2015), resveratrol (stilbenoid) (Gomes et al. 2018), Smilagenin (saponin) (He et al. 2019) are some of the non-flavonoid polyphenols with neuroprotective effects.

Phenolic acids containing Cinnamic acid derivatives (P-coumaric, Ferulic acid, Caffeic) and benzoic acid derivatives (protocatechuic acid, gallic, vanillic) have been reported to improve neurological dysfunctions by affecting neural and glial cells directly (Nabavi et al. 2015; Szwajgier, Borowiec, and Pustelniak 2017).

Tannins are known as a group of water-soluble polyphenols that can combine to the proteins. Tannins with low molecular weight have been classified as pseudo-tannins and tannins with the molecular weight of 1000 to 5000 Da have been named as true tannins. True tannins are classified into complex tannins, condensed tannins, and hydrolyzable tannins. Hydrolyzable tannins have been subdivided into ellagitannins and gallotannins as they are formed by hexahydroxy-diphenic acid and gallic acid units respectively (Table 1).

Polyphenols perform their neuroprotective functions via a number of variant mechanisms like scavenging of reactive oxygen and nitrogen species, inhibition of generation and aggregation of beta-amyloid, activation of redox-responsible transcription factors, regulation of the mitochondrial apoptosis system and regulation of gene's expression. In fact, a couple of mechanisms may play a role in the neuroprotection property of polyphenols depending on the various factors, including the structure of a compound and the disease (Rehman et al. 2019).

In the following, several studies to more explanations of beneficial effects and possible mechanisms of different polyphenols in neurodegenerative diseases are mentioned. In the study of Jiaqing and et al. the advantageous activity of Curcumin on the rat's model of PD was investigated. Results emphasized that Curcumin neuroprotective effects and properly diminished the 6-OHDA-induced neurotoxicity upregulation of the expressions of hippocampal TrkB, BDNF, and phosphatidylinositide 3-kinases (PI3K) (Yang et al. 2014). Besides, variant nanoformulation of Curcumin could improve the condition of the patient with MS and ALS by affecting the function and frequency of regulatory T-cell, the levels of Interleukin 10 (IL-10), Forkhead Box P3 (FOXP3), and Transforming growth factor beta (TGF-β) expression, and inflammatory mediators (Ahmadi et al. 2018; Dolati et al. 2018, 2019). Furthermore, increasing the expression of signal transducer and activator of transcription 5 (STAT5), JAK3, FOXP3, as well as increasing the levels of IL-10, TGF-β; moreover, activation and induction of Tregs mentioned as the main in vitro neuroprotective effects of Silymarin (Shariati et al. 2019). It was reported that the $6-$OHDA induced neurotoxicity meaningfully suppressed by Hesperidin via decreasing the level of reactive oxygen species (ROS), increasing the upregulation of gsk3β, polg, lrrk2, and casp9, and enhancing the levels and activity of superoxide dismutase (SOD), catalase (CAT), and GSH in

the in vitro and in vivo models of PD (Kesh et al. 2021). In a similar study, Hesperetin treatment significantly protects SH-SY5Y cells versus 6 − OHDA-induced neurotoxicity through activation of the nuclear erythroid 2-related factor 2/antioxidant response element (NRF2/ARE) signaling pathways, suppressing the apoptosis presses, diminishing the levels of cleaved caspase-3, −9, malondialdehyde (MDA) and ROS levels, as well as enhancing the levels and activity of Glutathione (GSH) and SOD (Li, Liu, et al. 2020). Also, reducing the activity of cholinesterase and production of ROS and MDA reported as the in vivo neuroprotective mechanism of Gallic acid in the Drosophila melanogaster model of AD (Ogunsuyi et al. 2020). Similarly, Naringenin like Hesperidin could significantly alleviate the in vivo and in vitro 6 − OHDA induced PD in a zebrafish model of PD and SHSY5Y cells through upregulation of casp9, lrrk2, and polg and decreasing the generation of ROS, and enhancing the levels and activity of CAT, GSH, and SOD (Kesh, Kannan, and Balakrishnan 2021). Naringenin showed in vivo neuroprotective effects against the neurotoxicity induced by AlCl3/D-galactose via suppressing the oxidative stress and decreasing the levels of acetylcholinesterase in the rat's model of AD (Haider et al. 2020). Moreover, the iron and rotenone-induced PD were satisfactorily suppressed with the combination treatment of Quercetin and Piperine. These polyphenolic agents showed their neuroprotective effects via attenuation of neuroinflammatory, increasing the levels and activity of variant neurotransmitter and antioxidant parameters (Sharma, Raj, and Singh 2020). Besides, Shamsher and et al. design a study to investigate the beneficial effects of intranasal delivery of resveratrol nanoparticles on the mice model of MS. Treatment with Resveratrol showed significant neuroprotective effects and leads to decreasing the retinal ganglion cell loss in an animal model of study (Shamsher et al. 2020). The MPP^+/MPTP-induced in vitro and in vivo PD alleviated by Ferulic acid via interfering with extracellular signal-regulated kinases (ERK)1/2-dependent Nrf2 signaling pathway that consequences to inhibition of SIRT2 activity, attenuation of oxidative stress (Li, Zhang, et al. 2020). Pelargonidin dose-dependently protected the rat model of parkinsonism via attenuation of oxidative stress, MDA content, and decreased the thiobarbituric acid reactive substances (TBARS) formation induced by 6-hydroxydopamine (6-OHDA) (Roghani et al. 2010). Moreover, the beneficial effect of coadministration of β-estradiol and Apigenin was investigated. Results demonstrated that Apigenin and β-estradiol decreased the symptoms of learning and memory impairment, number of β-amyloid plaques, as well as Caspase-3 expression in treated animals (Pirasteh et al. 2020). Quercetin is a bioflavonoid that showed the considerable neuroprotective and anti-inflammatory potential that numerous studies have confirmed its beneficial effects in neurodegenerative diseases. Interfering with the Nrf2/ARE and Nrf2/HO-1 and iNOS/NF-κB signaling pathway reported as the main neuroprotective mechanism (especially anti-AD activity) of quercetin (Bahar, Kim, and Yoon 2017; Li et al. 2019). A summary of important polyphenols and their appropriate advantages in neurodegenerative diseases is provided in Table 2. Chemical structures of selected phenolic compounds provided in Figure 1.

In summary, it seems that polyphenolic compounds, due to the presence of multiple hydroxyl groups in their structure, can significantly reduce oxidative stress, as one of the most important causes and exacerbates factor of neurodegenerative diseases, via increasing the levels and activity of CAT, SOD, GSH as well as decreasing the levels and activity MDA and ROS. As mentioned earlier, inflammation is another undeniable mechanism involved in the process of neurodegenerative diseases. In this regard, the remarkable ability of these compounds to control and alleviate the inflammation process through diminishing the expression of inflammatory factors such as cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF-α), IL-1β or IL-33, TGF-β, and IL-1α and affecting different pathways to inhibit the onset or exacerbation of the inflammatory process, as another important pharmacological and neuroprotective mechanism of polyphenols, always considered by researchers. Polyphenols can alter the levels of important neurotransmitters in the brain such as elevated levels of serotonin, dopamine, and acetylcholine, which may lead to improving the condition of patients with PD, AD, and other neurodegenerative diseases. These mechanisms are considered as the main protective effects of polyphenols, which are generally obtained by affecting and alteration with variant signaling pathways such as Nrf2/Keap1/ARE, PI3K/Akt/mTOR, TLR4/NF-kB, Nrf2/HO-1, Akt/Nrf-2, ERK1/2-Nrf2, and JAK2/STAT3. Effective markers in inflammatory and oxidative stress processes as the main influential factors in the incidence of neurodegenerative diseases as well as the reported neuroprotective effects of polyphenols due to interfering with these pathways are provided in Figure 2.

Stem cells potential for neuronal regeneration

In recent years, many efforts have been made to improve and enhance neurodegeneration, in the meantime stem cell therapy has played an undeniable and significant role. Stem cell therapy is one of the most important branches of regeneration medicine that has enhanced the researcher's hope to treat or improve the condition of the patient with varying debilitating diseases (Maxson et al. 2012; Luo et al. 2018). Mesenchymal stem cells (MSCs) have been well marked as multipotent cells that have significant ability to transform and differentiate into diverse tissue-forming cell lineages such as adipocytes, osteoblasts, tenocytes, chondrocytes, and myocytes (Maxson et al. 2012; Steward, Sridhar, and Meyer 2012; Luo et al. 2018). In addition to maintaining their ability to readily expand ex vivo for several passages, the multilineage differentiation susceptibility makes these cells a suitable option and useful system to improve the regeneration. Since these cells have a significant potential for both neuronal and glial differentiation, their use has been well-established for this therapeutic target of neurodegeneration (Maxson et al. 2012; Luo et al. 2018).

Table 2. Summary of important polyphenols and their appropriate advantages in neurodegenerative diseases.

Compound	Types of study	Cell line(s)/ animal model(s)	Type of Disease	Mechanism of action/ metabolic effects	References
Curcumin	In vivo	Sprague–Dawley rats' model of PD	Parkinson's disease	↑ Expressions of BDNF ↑ Expressions of TrkB ↑ Expressions of PI3K ↑ Activating BDNF/TrkB/ PI3K signal pathway	(Yang et al. 2014)
Curcumin	In vivo	Patients with MS	Multiple sclerosis	↓ STAT1 ↓ NF-κB ↓ AP-1 ↓ IL-1β ↓ IL-6 ↓ IFN-γ ↓ TNF-α ↑ Expression levels of Sox2 ↑ Expression levels of sirtuin-1 ↑ Expression levels of Foxp3	(Dolati et al. 2019)
Curcumin	In vivo	Patients with MS	Multiple sclerosis	↑ TGF-β and IL-10 mRNA and secretion levels ↑ Frequency of Treg cells ↑ Expression of TGF-β, FoxP3, and IL-10	(Dolati et al. 2018)
Curcumin	In vivo	Patients with ALS	Amyotrophic Lateral Sclerosis	↑ Probability of survival	(Ahmadi et al. 2018)
Silymarin	In vitro	Peripheral-blood mononuclear cells obtained from patients with MS	Multiple sclerosis	↑ Expression of STAT5 ↑ Expression of JAK3 ↑ Expression of FOXP3 ↑ Levels of TGF-β ↑ Levels of IL-10 ↑ Activation of T_{regs}	(Shariati et al. 2019)
Hesperidin	In vitro, In vivo	Zebrafish model of PD Human neuroblastoma cell lines (SH-SY5Y)	Parkinson's disease	↓ ROS level ↑ Upregulation of gsk3β, polg, lrrk2, and casp9 ↑ Levels and activity of SOD ↑ Levels and activity of CAT ↑ Levels and activity of GSH	(Kesh, Kannan, and Balakrishnan 2021)
Hesperidin	In vitro	Human neuroblastoma cell lines (SH-SY5Y)	Parkinson's disease	↑ Activation of the NRF2/ARE signaling pathways ↓ Apoptosis ↓ Caspase-3 and −9 ↓ MDA level ↓ ROS level ↑ Levels and activity of SOD ↑ Levels and activity of GSH	(Li, Liu, et al. 2020)
Gallic acid	In vivo	Drosophila melanogaster model of AD	Alzheimer's disease	↓ MDA level ↓ ROS level ↓ Activity of cholinesterase	(Ogunsuyi et al. 2020)
Naringenin	In vitro, In vivo	Zebrafish model of PD Human neuroblastoma cell lines (SH-SY5Y)	Parkinson's disease	↑ Upregulation of casp9, lrrk2, and polg ↓ ROS level ↑ Levels and activity of SOD ↑ Levels and activity of CAT ↑ Levels and activity of GSH	(Kesh, Kannan, and Balakrishnan 2021)
Naringenin	In vivo	Morris water maze rats' model of AD	Alzheimer's disease	↑ Dopamine level ↑ Serotonin level ↑ Glutathione peroxidase activity ↑ Levels and activity of CAT ↑ Levels and activity of SOD ↑ Levels and activity of GSH ↓ MDA level ↓ Expression of AChE gene	(Haider et al. 2020)
Quercetin	In vivo	Wistar rats' model of PD	Parkinson's disease	↓ MDA level ↓ Nitrite level ↓ GSH level	(Sharma, Raj, and Singh 2020)

(*continued*)

Table 2. Continued.

Compound	Types of study	Cell line(s)/ animal model(s)	Type of Disease	Mechanism of action/ metabolic effects	References
				↓ TNF-α levels ↓ IL-1β levels ↓ IL-6 levels ↑ Dopamine level ↑ Norepinephrine level ↑ Serotonin level	
Resveratrol	In vivo	Mice model of MS	Multiple sclerosis	↓ Retinal ganglion cell loss	(Shamsher et al. 2020)
Ferulic acid	In vitro, In vivo	Human neuroblastoma cell lines (SH-SY5Y) C57BL/6J mice	Parkinson's disease	↓ SIRT2 activity ↓ Oxidative stress ↑ Activation of the Nrf2/ ARE signaling pathway	(Li, Liu, et al. 2020)
Pelargonidin	In vivo	Rat's model of parkinsonism	Parkinson's disease	↓ Oxidative stress ↓ MDA content ↓ TBARS formation	(Roghani et al. 2010)
Apigenin	In vivo	Wistar rats' model of AD	Alzheimer's disease	↓ Learning and memory impairment ↓ β-amyloid plaques ↓ Caspase-3 expression	(Pirasteh et al. 2020)
Quercetin	In vitro, In vivo	Sprague-Dawley male rats, Neuroepithelioma cell line (SK-N-MC)	Alzheimer's disease	↑ CAT ↑ SOD ↓ MDA ↑ GSH levels ↓ ROS ↓ iNOS/NF-κB pathway ↓ HO-1/Nrf2 pathway	(Bahar, Kim, and Yoon 2017)
Quercetin	In vivo	Male Sprague-Dawley rats' model of AD	Alzheimer's disease	↑CAT ↑SOD ↓MDA ↑GSH levels ↑Nrf2/HO-1 pathway	(Li et al. 2019)

In 2019, Hoveizi et al. tried to differentiate mouse embryonic stem cells (MESCs) to neuron-like cells; for this reason, they used SB431542 small molecule on nanofibrous electrospun nanofibrous polylactic acid/Chitosan/Wax (PLA/CS/Wax) scaffold. After 20 days, the numbers of neural structures and neural markers such as NF-H, Nestin, Map2, and Tuj-1 were increased in a neural induction medium containing SB431542 in MESCs, cultured on designed scaffolds in comparison to the control group (Hoveizi and Ebrahimi-Barough 2019). Chiu et al. investigated the effect of human interleukin-12p80 (hIL12p80) on the regeneration of the sciatic nerve in mice. Results showed the recovery of the sciatic functional index, rotarod analyses and compound muscle action potential in NSCs that were transplanted with hIL12p80 were the best in comparison to the other groups. These advantages emphasize that NSCs together with hIL12p80 can increase the functional recovery and catalyze the regeneration of damaged nerves (Nouri et al. 2019). In the same study, IL12p80 triggered Schwann cell differentiation of the mouse NSCs and increased and improved the diameter of regenerated nerves and functional recovery in the animal model of sciatic nerve injury (Lee et al. 2017). In another study Masgutov et al. embedded the MSCs derived from adipose tissue in fibrin glue for the modes of sciatic nerve injury. Results emphasized that MSCs transplanted in fibrin glue could get into the nerve and migrate mainly retrogradely after transplantation. In addition, the stimulated myelination and axon growth and consequential neuroprotective effect on DRG L5 sensory neurons were observed (Masgutov et al. 2019). Furthermore, Weiwei et al. tried to benefit from the significant differentiation potential of human umbilical cord MSCs (hUC-MSCs) and improved the release of acetylcholine via inducing differentiate hUC-MSCs into cholinergic like neurons. For this reason, the beneficial effect of the BDNF-modified hUC-MSCs-derived cholinergic-like neurons in rat's model of AD was studied. Results demonstrated that transplantation of a new system could notedly improve memory abilities, spatial learning, promoted neurogenesis, inhibited neuronal apoptosis, enhanced release and hippocampal level of acetylcholine and decreased the expression of Aβ (Hu et al. 2019). To inhibit seizures and epileptiform discharges in animal models of epilepsy, Kaya et al. attempted to directly control the differentiation of NSCs into GABAergic cells and investigate their effects via intrahippocampal transplantation. In comparison to the control group, the GABAergic neuron group showed a considerable reduction in duration and overall frequency of spontaneous recurrent seizures and remarkable enhancement of GABA concentrations in the hippocampus (Xu et al. 2019). Furthermore, promoting neural stem/progenitor cells proliferation in the natural nerve conduits with anchored bFGF showed convenient effects and appropriate advantages like nerve autografting (Ma et al. 2017). Faghih et al. induced human adipose tissue-derived stem cells (hADSCs) (in serum-free and low-serum conditions) to dopamine-secreting cells as a suitable therapeutic strategy to increase dopamine levels in patients with PD. ADSCs successfully differentiated in both conditions and could express the variant dopaminergic and neuronal markers. The higher amount of dopamine and dopaminergic markers was found in the serum-free neurobasal condition (Faghih et al. 2019). Moreover, to find the new approach for treating the spinal

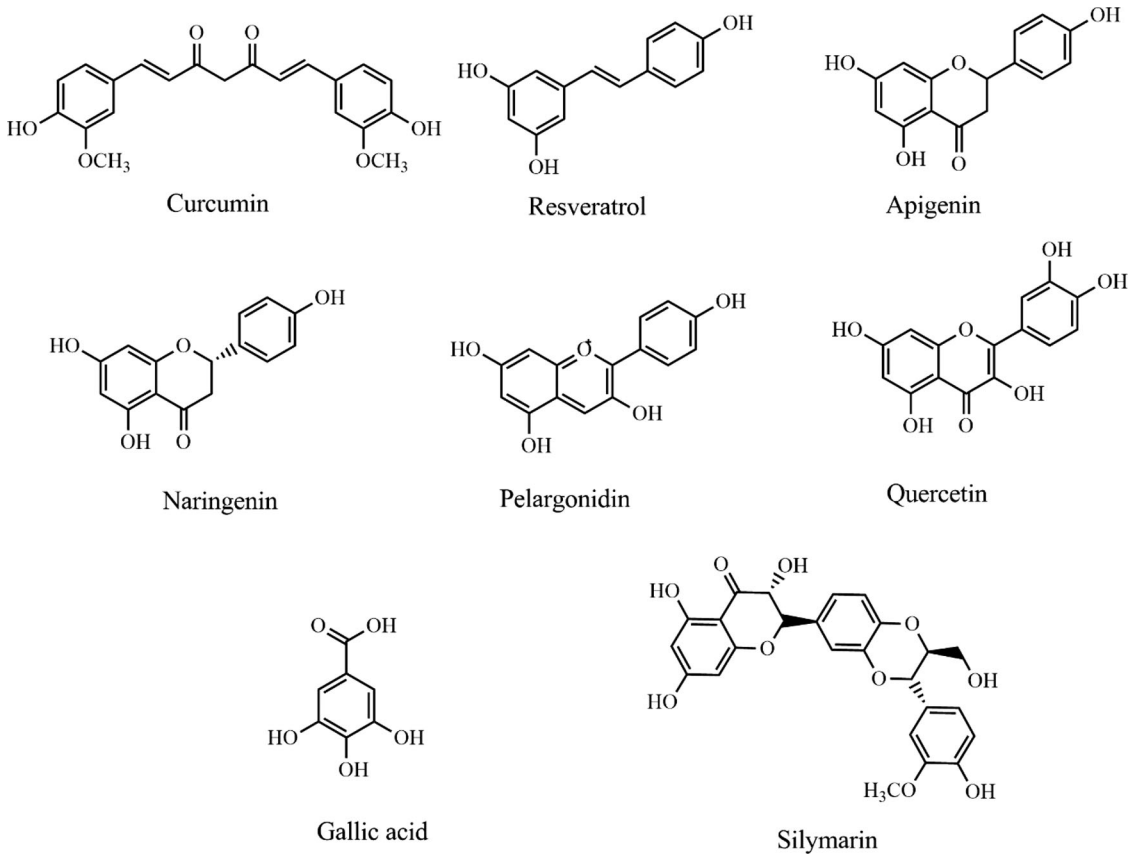

Figure 1. Chemical structures of selected phenolic compounds.

cord injury, Bagher et al. investigated the differentiation potential of olfactory ectomesenchymal stem cells into motor neuron-like cells. The results were acceptable and appropriate (Bagher et al. 2018).

Chemical stimulations for neuronal regeneration

The use of growth factors in tissue engineering has been suggested for triggering and promoting nerve regeneration. The neurotrophic growth factors, a classical growth factor family, contribute to the surviving and differentiating of nerve fibers in nervous systems via attaching to the particular cell-surface receptors that signal the neuron. Nerve growth factor (NGF) is a member of the neurotrophic factor's family that enhanced the axonal sprouting and neurite outgrowth of neurons. BDNF, another member of the neurotrophin family, was purified from mammalian brain. Now, NGF, BDNF, neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) form the neurotrophin family in mammals. Clearly, neurotrophic factors support neural survival after damage, but quantitative assessments, especially in axonal regeneration are necessary. The balance between the positive and negative signals of growth factors determines the regeneration and functional recovery after damage (Önger et al. 2017). NGF has a cytoprotective effect and stimulates the outgrowth of neuritic projections. However, the direct administration of exogenous NGF is not useful because of the poor penetration of the polar peptide to the blood-brain barrier and its rapid degradation. Therefore, the search for induction of NGF by small-molecules for stimulating natural production instead of the administration of the peptide is necessary. It was shown that erinacines and scabronines stimulated NGF synthesis activity significantly. The core structure of these two diterpenoid natural products is similar to the cyathin class of antibiotics (Wright et al. 1999). Another in vitro study showed that the cellular pool of NGF mRNA in fibroblast's cells was increased by 1, 25-Dihydroxyvitamin D, (1, 25-(OH)2, D3) in a concentration-dependent manner about three hours after 1, 25-(OH)2, D3 addition and this persisted for 28 hours. Moreover, the concentration of NGF in the cell culture medium was increased. In addition, the effect of 1, 25-(OH)2, D3 on c-fos expression was analyzed. Results showed that there is not c-fos expression in the presence of 1, 25-(OH)2, D3 and suggested that 1, 25-(OH)2D3 enhanced the pool of NGF mRNA by a mechanism independent of the c-fos pathway. This indicated a possible therapeutic potential for 1, 25-(OH)2, D3 in neurodegenerative diseases (Wion et al. 1991).

Tissue engineering for neuronal regeneration

The repair or replacement of damaged nerve cells is fundamental in nervous system regeneration. Lower organisms have good abilities to regenerate nerve cells, but higher organisms, like humans, have a few capacities in neural regeneration. Neuron injury in adulthood may reverse a regenerative state in the PNS, but neurons from the CNS have a much lower capacity for regenerative growth (Doron-

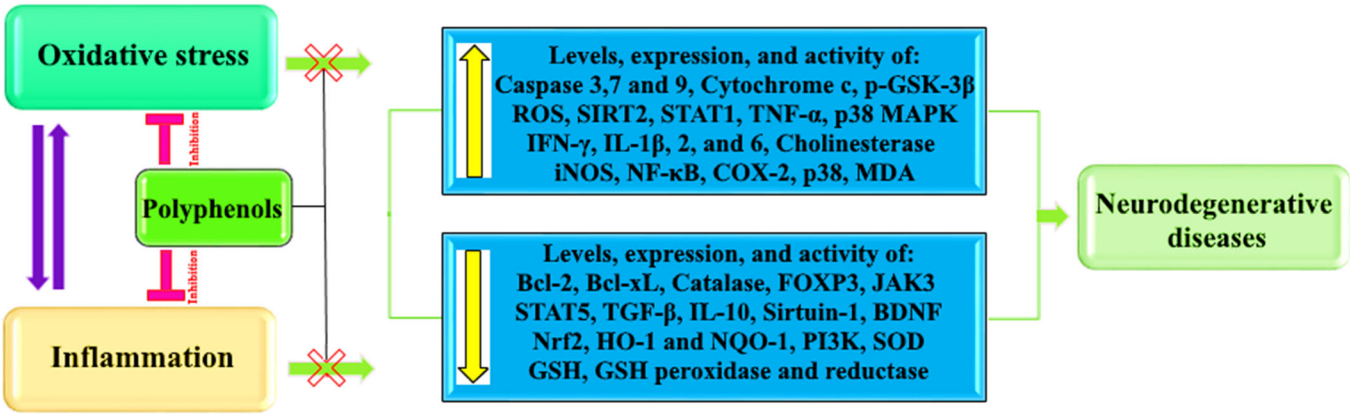

Figure 2. Effective markers in the inflammatory and oxidative stress processes as the main influential factors in the incidence of neurodegenerative diseases as well as the reported neuroprotective effects of polyphenols due to interfering with these pathways.

Mandel, Fainzilber, and Terenzio 2015). Neural tissue engineering and regenerative medicine are related to neuroscience, cell biology, and engineering, and these sciences are combined to help the regeneration or repair of damaged neural tissues. Cells, biomaterial scaffolds, and bioactive agents contribute to nervous system repair in various ways (Zhang and Wen 2009).

Gene therapy for neuronal regeneration

Neurological disorders encompass a wide range of diseases, including PD, AD, MS, HD, stroke, brain or spinal cord injury and ALS. Existing strategies such as drug therapy or the use of biological therapies cannot treat or cure these diseases well. In this regard, some studies have used effective, benign and noninvasive approaches based on the delivery of drugs, proteins, and genes to treat or slow the progression of these diseases (Su et al. 2009; Geldenhuys et al. 2011; Chaturvedi et al. 2014). Gene and cell-based therapies are used to stop and slow down brain cell death, which is a hallmark of most degenerative neuropsychiatric disorders. The progress of neurological diseases can be stopped or slowed by targeting specific types of cells such as astrocytes and neurons. Because gene therapy can result in long-term or transient gene expression in certain cell types, this treatment can be very useful in this regard. The basis of gene therapy is the use of nucleic acids as a pro-drug which has the potential to modulate the therapeutic protein expression inside the cells. With this interpretation, gene therapy has been suggested as a way to increase the neurotrophic factors local expression and in restoring the functional properties of damaged neurons under varied neuropathic diseases (Pêgo, Oliveira, and Moreno 2013). Recently, gene-based therapies for the neurodegenerative disease have received much attention, and various genes have been delivered to cells in the CNS. Utilization of modified cells expressing the genes of variant growth factors such as fibroblast growth factor-2 (FGF2), insulin-like growth factor-1 (IGF1), BDNF, vascular endothelial growth factor (VEGF), angiogenin (ANG) and glial cell-derived neurotrophic factor (GDNF) with neurotrophic functions have had some effects (Blesch and Tuszynski 2009). Strategies of gene delivery in neurodegeneration treatments fall into three categories: Augmentation, Silencing, and Editing. The purpose of these methods is to alter the expression of the target gene and restore/repair disturbed CNS homeostasis. In general, targeted gene delivery systems to the CNS should enhance the neuroprotective effects. For example, rendering neurotrophin genes or reversing the mechanisms of neurotoxicity, such as the prevention of neuronal inflammatory biomarker gene expression and repair of CNS homeostasis. The most common gene delivery systems are viral vectors and nanoparticles. In addition to delivering the gene to brain cells, viral vectors are also used to transmit genes to cardiac, cancer and muscle cells (Cerullo et al. 2010; Katz et al. 2013; Wang et al. 2014). These vectors exploit the virus's ability to infect mammalian cells and use the host system to generate viral proteins. Construction of a viral vector involves replacing genes of interest with segments of the viral immune genome (Joshi, Labhasetwar, and Ghorpade 2017). Herpes-simplex virus (HSV), adenoviruses, lentiviruses, adeno-associated viruses (AAV), and have been used to transmit transient genes in studies (Glatzel et al. 2000; Chattopadhyay et al. 2005; Towne et al. 2009; Yu et al. 2011). Although the effects of different types of metallic nanoparticles containing iron, silica, and silver on brain cells have been studied (Klejbor et al. 2007; Geppert et al. 2011; Luther et al. 2011; Pilakka-Kanthikeel et al. 2013), nonmetallic polymeric nanoparticle systems have often been used for gene delivery (Wong, Wu, and Bendayan 2012). Various types of polymeric, liquid-solid nanoparticles, liposomes and nanoemulsions along with optimization strategies of gene delivery and expression have been documented in the literature (Wong, Wu, and Bendayan 2012; Shah, Yadav, and Amiji 2013; Tosi et al. 2013). One of the benefits of gene delivery as a tool for implementing therapeutic interventions in delayed or prolonged cell death in some disorders is the continuation of protein synthesis over a long duration of time, thereby reducing the need for repeated and frequent drug interventions (Craig and Housley 2016). In recent years, multifunctional systems for gene delivery have been developed to address gene delivery problems such as DNA release, endosomal escape and premature unpackaging (Tan et al. 2016). Lopes and colleagues developed neuron-targeted non-viral

gene carriers to deliver therapeutic genes for peripheral neuropathy treatment. They used thiolated trimethyl chitosan (TMCSH) polymeric nanoparticles to deliver BDNF in the model of peripheral nerve injury. This nanoparticle-mediated gene delivery is designed to protect the damaged neurons from prolonged degeneration and speed up the regeneration of nerves. The results showed that the TMCSH-HC/BDNF nanoparticles enhanced the release and expression of the gene in neural tissues. Additionally, as a result of treatment with the designed system, the density of myelinated axons in the distal stump of the injured nerve is higher, and the density of these axons is preserved (Lopes et al. 2017).

In a 2017 study by Chen et al., The positive charge oligo [poly (ethylene glycol) fumarate] (OPF+) hydrogel was used to repair the spinal cord injury. This hydrogel-based scaffold was used to deliver Schwann cells alone and with a GDNF for four weeks as an implant in a rat spinal cord. Scaffold containing GDNF factor enhanced axonal regeneration compared to scaffold containing Schwann cells. Furthermore, in the case of GDNF-SC, the myelination of the regenerated axons was enhanced. Implantation of GDNF-SCs into the scaffold OPF + led to an increase in the number of total axons, myelinated axons and the proportion of mature myelinated axons (Chen et al. 2018).

For the treatment of ALS, human umbilical cord blood mononuclear cell (hUCBMC) with adenoviral vectors was applied for the simultaneous delivery of three therapeutic genes, including GDNF, VEGF and neural cell adhesion molecule (NCAM) into damaged neurons of the spinal cord. The efficacy of this treatment was evaluated by measuring life expectancy, behavioral tests and immunofluorescence analysis of homing, survival and gene expression. Assessment of gene transfer into mice blood showed high levels of hUCBMCs homing and survival in the spinal cord. This study demonstrates the increased homing and viability of transplanted triple cells in the spinal cord, confirming the therapeutic ability of hUCBMCs in the neurotrophic factors over expression (Islamov et al. 2017).

Limong and his colleagues used the micropillared 3 D scaffold made of poly-ε-caprolactone (PCL) degradable synthetic biopolymer to allow growth and maturation of nerve cells through controlled release of BDNF. The three-dimensional structure of the designed system increased the delivery of bioactive molecules to neurons and neurotrophin release for 21 days. Also, due to an enhanced continuous release of the neurotrophic factor by the system designed, the growth of neural cells and their survival have been improved (Limongi et al. 2018).

A scaffold made of alginate hydrogels containing Schwann cells was used to reconstruct axons located in the lateral hemisection lesion in the rat spinal cord. For this purpose, after transections of the spinal cord, hydrogels containing Schwann cells were transplanted into the lesion site, and BDNF was injected caudally by a viral vector. This combined method enhanced the descending axonal growth and penetration of axons into the host parenchyma in the lesion. The number of regenerated axons also increased through transient expression of viral neurotrophin with the injection of Schwann cells into the host parenchyma (Liu et al. 2017). A 3 D scaffold made of PCLEEP-collagen hybrid hydrogel was used as a platform for the treatment of nerve damage. It is designed for non-viral delivery of nucleic acids and proteins (NT-3 and miR-222) to enhance neuronal regeneration and remyelination after spinal cord injury in the rat spinal cord. Imparted topographic signals of the nanofibers develop neurite and support remyelination within lesion sites (Nguyen et al. 2017). Multifunctional progranulin protein (PGRN) has a prominent role in modulating CNS inflammation and also acts as a neuronal autocrine growth factor. It activates cellular signaling pathways that regulate oxidative stress, excitotoxicity, amyloidogenesis, and synaptogenesis, and these important roles indicate the potential of this protein in targeted treatment of neurodegenerative disorders such as AD. The use of PGRN gene transfer though lentiviral vectors in a mouse model of AD have been reported by Van Kampen et al. in 2017. Viral vector delivery of this gene substantially enhances gene expression in the neuronal hippocampus. This enhanced gene expression reduced the burden of amyloid plaques in mice and also reduced the markers of synaptic atrophy and inflammation (Van Kampen and Kay 2017).

Polyphenols for neuronal regeneration

As previously mentioned, polyphenolic antioxidants can exert consequential neuroprotective effects and play an influential role in the treatment of neurodegenerative diseases via their significant potential in free radical scavenging, which is one of the major contributors to neuronal damage. To date, in many studies, polyphenolic antioxidants have shown a notable neuroprotective activity and have been helpful for neuronal regeneration; for this reason, they were one of the important tools for the treatment of neurodegenerative diseases.

In 2019, Zhou et al. investigated the effect and fundamental mechanism of action of luteolin (a natural flavonoid) on neurogenesis in the Ts65Dn mice which served as a model of Down syndrome. Behavioral performance in Ts65Dn mice significantly improved, and this effect may be associated with neuronal differentiation and commutation in hippocampal neurogenesis. Advantages suggest that luteolin can promote neuronal proliferation (Zhou et al. 2019). Furthermore, Katebi et al. introduced a new approach for neuronal repair therapeutics. They concluded that quercetin and NGF in combination with superparamagnetic iron oxide nanoparticles could efficiently promote the neuronal branching in morphogenesis of PC12 cells (Katebi et al. 2019). Besides, to increase the restoration of neuronal connectivity subsequent to injury of the CNS, Bieler et al. investigated the in vitro effects and suitable potential of a prenylflavonoid. Enhancement of neuronal differentiation factor 1 (ENDF1) was segregated from hops to promote regeneration of rat dorsal root ganglion neurons in the presence of several axon growth inhibitors. Regardless of the attendance of inhibitors, ENDF1 could notedly promote branching in

dorsal root ganglion neurons and induce the percentage of sensory neurons able to regrow their neurites (Bieler et al. 2019). In 2019, Samadian et al. designed a new scaffold using collagen hydrogel containing naringin, as a flavanone glycoside, for peripheral nerve damage treatment. The in vitro advantages suggested that in comparison with the control group the proliferation of Schwann cells on the new system, collagen/naringin hydrogel, was meaningfully higher. Besides, the animal studies aboveboard emphasized that the naringin-incorporated collagen hydrogel could be an encouraging subsidiary approach to treat nerve damages (Samadian et al. 2019). In the same way, Baicalein (is a flavone) increases the impression of low dose levodopa on the gait deficits and showed suitable neuroprotection and enhanced the regeneration of dopaminergic neurons (Zheng et al. 2019). Besides, Chen et al. investigated the potential of liquiritin (the 4′-O-glucoside of the flavanone liquiritigenin) to induce the neurite outgrowth. Liquiritin could appreciably promote the neurite outgrowth induced via NGF in PC12 cells (Chen et al. 2009). Icariin (a prenylated flavonol glycoside) is a neuroprotective compound that could notedly promote the proliferation and growth of NSCs obtained from the rat hippocampus (Fu et al. 2018). In a similar study, the potential of icariin in the restoration of myelin after acute demyelination on C57BL/6 mice was investigated. Icariin could significantly improve the remyelination process, increase NF200-positive axons repair, and prevent the neuron-derived neurotrophic factor loss (Zhang et al. 2017). In 2016, Chang et al. administrated intrathecally flavopiridol (Alvocidib; also known as flavopiridol is a flavonoid alkaloid CDK9 kinase inhibitor) in an animal model of spinal cord injury. Flavopiridol could improve neuronal regeneration and enhance performance. In addition to enhancement in the survival of the neurons, it could significantly inhibit the proliferation and migration of astrocytes (Li et al. 2016). Pluripotent stem cells that were treated with 3,2-dihydroxyflavone in an in vivo investigation displayed augmented pluripotency marker expression, proliferation and neuroprotective attributes and properties of benefits than controls in the peripheral nerve injury model (Han et al. 2015).

Moreover, the beneficial effect of flavonoids obtained from the leaves and stems of *Scutellaria baicalensis* Georgi in an in vitro model of neural cell apoptosis were investigated. Results suggest that flavonoids inhibited cell apoptosis, improved cell survival and the activities of GSH peroxidase and superoxide dismutase (Miao et al. 2014). In the study of Junxiong and et al. the in vivo advantages and potential of Curcumin on the promotion of functional recovery and neural regeneration after sciatic nerve injury were investigated, and results emphasized that Curcumin could properly promote nerve regeneration and leads to an increase in sensory and motor function recovery in the diabetic rats' models of nerve injury (Ma et al. 2016). In a similar study, curcumin nanoparticles could significantly increase the regeneration of sciatic nerves in male Wistar rats (Jahromi et al. 2020). Besides, the synthesized nanoparticles of Naringin and Berberine in combination with a hydrogel of chitosan/alginate lead to in vivo and in vitro increases in the regeneration of the peripheral nerve and notedly elevated the motor and sensory functional recovery (Ebrahimi et al. 2020). Moreover, inhibition of $p75^{NTR}$, MAPK, and Caspase 3 and JNK pathways was suggested as the main neuroprotective mechanism of Naringenin that leads to facilitate the regeneration of sciatic nerve and improve the recovery of motor and sensory function in the mice model of peripheral nerve injuries (Oliveira et al. 2020). Besides, spinal cord injury is another neuronal related condition that leads to severe physical disabilities, intense psychological damage as well as reduced quality of life. Variant studies have examined the protective effects of polyphenol compounds in improving the pathophysiological condition and restoration of damaged neurons after spinal cord injury, accordingly, interfering with various signaling pathways such as the Keap1-Nrf-2/HO-1, PI3K/Akt/mTOR, ERK1/2-Nrf2, TGF-β/Smad, JAK2/STAT3, MAPK/JNK-NF-κB, and ERK/NADPH oxidase have been suggested as the main signaling pathways that lead to neuroprotective effects of polyphenol after spinal cord injury (Khalatbary 2014; Lin, Huo, and Liu 2017; Coyoy-Salgado et al. 2019).

Similarly, various studies have shown the positive neuroprotective effects of polyphenolic compounds such as myricetin, quercetin, tannic acid and naringenin on in vivo and in vitro experiments (Ramezani et al. 2016; Chen et al. 2017; Goes et al. 2018; Kujawska and Jodynis-Liebert 2018; Monfared, Ghaee, and Ebrahimi-Barough 2018).

Importance, challenges, and future perspective

Nervous system injuries affect over 90,000 people every year (Stabenfeldt, García, and LaPlaca 2006). It is an approximation that in the US, spinal cord injuries alone affect 12,000 each year (Ruppert, Olson, and Cox 2019). Loss of neurological sensory tissues due to various disorders or physical injuries can have a profound effect on the patient's life and cause disability. In recent years, the inability to fully or appropriately improve and restore functional abilities in patients with neuronal damage has been a major challenge for many scientists. The nervous system consists of two parts, the brain and spinal cord which are called the CNS, and the PNS respectively. Most of the CNS is unable to regenerate and self-repair while the PNS has a natural intrinsic capability for regeneration and repair (Yiu and He 2006; Mahar and Cavalli 2018).

Many endeavors have been made to understand the mechanisms involved in neuronal regulation as well as to stimulate the growth of neurons in vivo and in vitro. In this regard, different strategies have been proposed to achieve this goal and enable researchers to restore the functions after an injury to patients. These numerous efforts that were dedicated to advancement in experimental spinal cord injury treatments, lead to the introduction of new approaches like cell transplantation (neural transplantation), antioxidative and anti-inflammatory molecules, growth-factors or molecules to increase neurite growth and molecules that relieve an inhibitory environment or glial scarring to guide and

improve nerve regrowth. Proposed solutions should be reliably evaluated for efficacy, safety, and immunological parameters before use. Little progress has been made in clinical trials, and a limited number of studies have been able to show good clinical results. So, there is currently no treatment option for recovering human nerve function after injury to the CNS (Yiu and He 2006; Mahar and Cavalli 2018; Kubinová 2020). The role of "regenerative medicine" in this path is undeniable, and especially the branches of gene therapy and stem cell therapy have raised hopes for greater future improvements. The importance of neuronal regeneration becomes even greater when parts of the pathogenesis of neurodegenerative diseases such as MS and ALS occur through neuronal degeneration and finding a new effective way to re-grow neurons in the CNS can improve and transform the lives of millions of patients with neurodegenerative diseases and neuronal injuries (Bucchia et al. 2018).

Conclusion

Damaged tissues and neurodegenerative diseases like PD, AD, MS, HD, stroke, brain or spinal cord injury and ALS form a part of clinical conditions that are still not cured completely by modern treatment. Injury to the brain and spinal cord has very little chances of being cured. AD, PD and other neurodegenerative diseases are only treatable symptomatically and the person suffering from these diseases has to bear them lifelong. Damage to organs and neurodegenerative diseases forms a source of tremendous suffering and disability to the patient concerned as well as to the caregivers of the patient. Currently, only allopathic drugs and organ transplantation are the available options for the therapy of the above complications. However, they provide no complete relief in the majority of the cases.

Surgical procedures can be used, but they have their own limitations. Stem cell therapy is now being practiced at higher medical centers for the cure of various ailments, but it's still a new field that is very expensive and available to only a few patients. Thus, in future molecules with regenerative capacity like peptides, cytokines, polyphenolic antioxidants need to be used to treat the complications of neurodegenerative diseases. Polyphenolic antioxidants can help in the scavenging of free radicals and prove to be beneficial in neurodegenerative diseases since there is the involvement of free radicals in the development of neurodegenerative diseases. They also provide a neuroprotective effect. Polyphenolic compounds have been used for a very long time in traditional medicine for the cure of various neurodegenerative diseases. Polyphenolic phytochemicals can thus form a reliable and affordable treatment of neurodegenerative diseases. Quercetin, hesperetin, naringin, icariin, liquiritin, ellagitannins, etc. are some compounds that can provide very great results in the therapy of neurodegenerative diseases. Peptides, cytokines, etc. Administered exogenously can also help in tissue regeneration and neurodegenerative diseases since these molecules are involved with the repair process in the body. The introduction of stem cells inside the body is also a new approach that can help in the regeneration process since it can rapidly expand and help in the formation of the desired tissue that has been degenerated. The chemical stimulation technique will also change the future of therapeutics since they will help in the development of factors responsible for the growth and differentiation of nerve fibers. Moreover, tissue engineering is a new concept by which tissues will be healed and regenerated by using advanced robotic techniques. Gene therapy will help in the manipulation of genes, which will help in combating neurodegenerative diseases since many neurodegenerative diseases involve one or more defective genes. All these techniques need to be developed to a great extent so that proper cure is achieved with these techniques in case of damaged organs or neurodegenerative diseases. Also, the above-mentioned regenerative molecules, phytochemicals, and techniques have to be evaluated thoroughly in animals and humans for their beneficial effects. In the future, the above-mentioned techniques along with different regenerative molecules and phytochemicals alone or in combination with each other will someday help in the treatment of damaged tissues and neurodegenerative diseases.

Conflicts of interest

Authors declare that they have no conflicts of interest.

Acknowledgements

This article is the outcome of an in-house financially non-supported study.

Abbreviation

1,	25-Dihydroxyvitamin D
(1, 25-(OH)2, D3)	6-hydroxydopamine
(6-OHDA)	Adeno-associated viruses
(AAV)	Alzheimer's disease
(AD)	Amyotrophic lateral sclerosis
(ALS)	Angiogenin
(ANG)	Brain-derived neurotrophic factors
(BDNF)	Catalase
(CAT)	Central neuron system
(CNS)	Cyclooxygenase-2
(COX-2)	Epidermal growth factor
(EGF)	Epigallocatechin-3-gallate
(EGCG)	Extracellular signal-regulated kinases
(ERK1/2)	Fibroblast growth factor-2
(FGF2)	Forkhead Box P3
(FOXP3)	Glial cell-derived neurotrophic factor
(GDNF)	Glutathione
(GSH)	Herpes-simplex virus
(HSV)	Human adipose tissue-derived stem cells
(hADSCs)	Human umbilical cord blood mononuclear cell
(hUCBMC)	Human umbilical cord MSCs
(hUC-MSCs)	Huntington's disease
(HD)	Insulin-like growth factor-1
(IGF1)	Interleukin-12p80
(hIL12p80)	Malondialdehyde
(MDA)	Mesenchymal stem cells
(MSCs)	Mouse embryonic stem cells
(MESCs)	Multifunctional progranulin protein
(PGRN)	Multiple sclerosis

(MS)	Nuclear erythroid 2-related factor 2/antioxidant response element
(NRF2/ARE)	Nuclear factor kappa-light-chain-enhancer of activated B cells
(NF-κB)	Nerve growth factor (NGF); Neural cell adhesion molecule
(NCAM)	Neural stem cells
(NSCs)	Neuronal differentiation factor 1
(ENDF1)	Neurotrophin-3
(NT-3)	Parkinson's disease
(PD)	Peripheral neuron system
(PNS)	Polylactic acid/Chitosan/Wax
(PLA/CS/Wax	Poly-ε-caprolactone
(PCL)	Reactive oxygen species
(ROS)	Signal transducer and activator of transcription 5
(STAT5)	Subventricular zone
(SVZ)	Superoxide dismutase
(SOD)	Thiobarbituric acid reactive substances
(TBARS)	Thiolated trimethyl chitosan
(TMCSH)	Transient ischemic attack
(TIA)	Transforming growth factor beta
(TGF-β)	Tumor necrosis factor alpha
(TNF-α)	Vascular endothelial growth factor
(VEGF)	

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References

Abeliovich, A., and A. D. Gitler. 2016. Defects in trafficking bridge Parkinson's disease pathology and genetics. *Nature* 539 (7628): 207–16. doi: 10.1038/nature20414.

Ahmadi, M., E. Agah, S. Nafissi, M. R. Jaafari, M. H. Harirchian, P. Sarraf, S. Faghihi-Kashani, S. J. Hosseini, A. Ghoreishi, V. Aghamollaii, et al. 2018. Safety and efficacy of nanocurcumin as add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a pilot randomized clinical trial. *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics* 15 (2):430–8. doi: 10.1007/s13311-018-0606-7.

Aras, A. B., M. Guven, T. Akman, A. Ozkan, H. M. Sen, U. Duz, Y. Kalkan, C. Silan, and M. Cosar. 2015. Neuroprotective effects of daidzein on focal cerebral ischemia injury in rats. *Neural Regeneration Research* 10 (1):146–52. doi: 10.4103/1673-5374.150724.

Bagher, Z., S. K. Kamrava, R. Alizadeh, M. Farhadi, M. Absalan, M. Falah, F. Faghihi, A. Zare-Sadeghi, and A. Komeili. 2018. Differentiation of neural crest stem cells from nasal mucosa into motor neuron-like cells. *Journal of Chemical Neuroanatomy* 92: 35–40. doi: 10.1016/j.jchemneu.2018.05.003.

Bahar, E., J. Y. Kim, and H. Yoon. 2017. Quercetin attenuates manganese-induced neuroinflammation by alleviating oxidative stress through regulation of apoptosis, iNOS/NF-κB and HO-1/Nrf2 pathways. *International Journal of Molecular Sciences.* 18 (9):1989. doi: 10.3390/ijms18091989.

Barreca, D., E. Bellocco, G. D'Onofrio, S. F. Nabavi, M. Daglia, L. Rastrelli, and S. M. Nabavi. 2016. Neuroprotective effects of quercetin: from chemistry to medicine. *CNS & Neurological Disorders Drug Targets* 15 (8):964–75. doi: 10.2174/1871527315666160813175406.

Beyar, R. 2011. Challenges in organ transplantation. *Rambam Maimonides Medical Journal* 2 (2):e0049. doi: 10.5041/RMMJ.10049.

Bieler, L., M. Vogl, M. Kirchinger, C. Urmann, H. Riepl, C. E. Bandtlow, L. Klimaschewski, L. Aigner, and S. Couillard-Despres. 2019. The prenylflavonoid ENDF1 overrules central nervous system growth inhibitors and facilitates regeneration of DRG neurons. *Frontiers in Cellular Neuroscience* 13:332. Doi: 0.3389/fncel.2019.00332. doi: 10.3389/fncel.2019.00332.

Blesch, A., and M. H. Tuszynski. 2009. Spinal cord injury: Plasticity, regeneration and the challenge of translational drug development. *Trends Neurosci* 32 (1):41–7. doi: 10.1016/j.tins.2008.09.008.

Braidy, N., B. E. Jugder, A. Poljak, T. Jayasena, S. M. Nabavi, P. Sachdev, and R. Grant. 2017. Molecular targets of tannic acid in Alzheimer's disease. *Current Alzheimer Research* 14 (8):861–9. doi: 10.2174/1567205014666170206163158.

Bucchia, M., S. J. Merwin, D. B. Re, and S. Kariya. 2018. Limitations and challenges in modeling diseases involving spinal motor neuron degeneration in vitro. *Frontiers in Cellular Neuroscience* 12(:61 doi: 10.3389/fncel.2018.00061.

Canter, R. G., J. Penney, and L.-H. Tsai. 2016. The road to restoring neural circuits for the treatment of Alzheimer's disease. *Nature* 539 (7628):187–96. doi: 10.1038/nature20412.

Cerullo, V., S. Pesonen, I. Diaconu, S. Escutenaire, P. T. Arstila, M. Ugolini, P. Nokisalmi, M. Raki, L. Laasonen, et al. M. Särkioja, 2010. Oncolytic adenovirus coding for granulocyte macrophage colony-stimulating factor induces antitumoral immunity in cancer patients. *Cancer Research* 70 (11):4297–309. doi: 10.1158/0008-5472.CAN-09-3567.

Chattopadhyay, M., D. Krisky, D. Wolfe, J. Glorioso, M. Mata, and D. Fink. 2005. HSV-mediated gene transfer of vascular endothelial growth factor to dorsal root ganglia prevents diabetic neuropathy. *Gene Therapy* 12 (18):1377–84. doi: 10.1038/sj.gt.3302533.

Chaturvedi, M., Y. Molino, B. Sreedhar, M. Khrestchatisky, and L. Kaczmarek. 2014. Tissue inhibitor of matrix metalloproteinases-1 loaded poly(lactic-co-glycolic acid) nanoparticles for delivery across the blood-brain barrier . *International Journal of Nanomedicine* 9: 575–88. doi: 10.2147/IJN.S54750.

Chen, B. H., J. H. Park, J. H. Ahn, J. H. Cho, I. H. Kim, J. C. Lee, M.-H. Won, C.-H. Lee, I. K. Hwang, et al. J.-D. Kim, 2017. Pretreated quercetin protects gerbil hippocampal CA1 pyramidal neurons from transient cerebral ischemic injury by increasing the expression of antioxidant enzymes. *Neural Regeneration Research* 12 (2):220–7. doi: 10.4103/1673-5374.200805.

Chen, B. K., N. N. Madigan, J. S. Hakim, M. Dadsetan, S. S. McMahon, M. J. Yaszemski, and A. J. Windebank. 2018. GDNF Schwann cells in hydrogel scaffolds promote regional axon regeneration, remyelination and functional improvement after spinal cord transection in rats. *Journal of Tissue Engineering and Regenerative Medicine* 12 (1):e398–e407. doi: 10.1002/term.2431.

Chen, Z-a, J.-L. Wang, R.-T. Liu, J.-P. Ren, L.-Q. Wen, X.-J. Chen, and G.-X. Bian. 2009. Liquiritin potentiate neurite outgrowth induced by nerve growth factor in PC12 cells. *Cytotechnology* 60 (1–3):125–32. doi: 10.1007/s10616-009-9226-8.

Chou, R., T. Dana, I. Blazina, M. Daeges, and T. L. Jeanne. 2016. Statins for prevention of cardiovascular disease in adults: Evidence report and systematic review for the US Preventive Services Task Force. *Jama* 316 (19):2008–24. doi: 10.1001/jama.2015.15629.

Cirmi, S., N. Ferlazzo, G. E. Lombardo, E. Ventura-Spagnolo, S. Gangemi, G. Calapai, and M. Navarra. 2016. Neurodegenerative diseases: Might citrus flavonoids play a protective role? *Molecules* 21 (10):1312. doi: 10.3390/molecules21101312.

Coyoy-Salgado, A., J. J. Segura-Uribe, C. Guerra-Araiza, S. Orozco-Suárez, H. Salgado-Ceballos, I. A. Feria-Romero, J. M. Gallardo, and C. E. Orozco-Barrios. 2019. The importance of natural antioxidants in the treatment of spinal cord injury in animal models: An overview. *Oxidative Medicine and Cellular Longevity* 2019:3642491 doi: 10.1155/2019/3642491.

Craig, A. J., and G. D. Housley. 2016. Evaluation of gene therapy as an intervention strategy to treat brain injury from stroke. *Frontiers in Molecular Neuroscience* 9:34. doi: 10.3389/fnmol.2016.00034.

Delcroix, G. J.-R., P. C. Schiller, J.-P. Benoit, and C. N. Montero-Menei. 2010. Adult cell therapy for brain neuronal damages and the role of tissue engineering. *Biomaterials* 31 (8):2105–20. doi: 10.1016/j.biomaterials.2009.11.084.

Dolati, S., M. Ahmadi, L. Aghebti-Maleki, A. Nikmaram, F. Marofi, R. Rikhtegar, H. Ayromlou, and M. Yousefi. 2018. Nanocurcumin is a

potential novel therapy for multiple sclerosis by influencing inflammatory mediators. *Pharmacological Reports* 70 (6):1158–67. doi: 10.1016/j.pharep.2018.05.008.

Dolati, S., Z. Babaloo, H. Ayromlou, M. Ahmadi, R. Rikhtegar, D. Rostamzadeh, L. Roshangar, M. Nouri, A. Mehdizadeh, et al. V. Younesi, 2019. Nanocurcumin improves regulatory T-cell frequency and function in patients with multiple sclerosis. *Journal of Neuroimmunology* 327:15–21. doi: 10.1016/j.jneuroim.2019.01.007.

Doron-Mandel, E., M. Fainzilber, and M. Terenzio. 2015. Growth control mechanisms in neuronal regeneration. *FEBS Letters* 589 (14): 1669–77. doi: 10.1016/j.febslet.2015.04.046.

Dzobo, K., N. E. Thomford, D. A. Senthebane, H. Shipanga, A. Rowe, C. Dandara, M. Pillay, and K. S. C. M. Motaung. 2018. Advances in regenerative medicine and tissue engineering: Innovation and transformation of medicine. *Stem Cells International* 2018:2495848. doi: 10.1155/2018/2495848.

Ebrahimi, M. H., H. Samadian, S. T. Davani, N. R. Kolarijani, N. Mogharabian, M. S. Salami, and M. Salehi. 2020. Peripheral nerve regeneration in rats by chitosan/alginate hydrogel composited with Berberine and Naringin nanoparticles: In vitro and in vivo study. *Journal of Molecular Liquids* 318:114226. doi: 10.1016/j.molliq.2020.114226.

Faghih, H., A. Javeri, H. Amini, and M. F. Taha. 2019. Directed differentiation of human adipose tissue-derived stem cells to dopaminergic neurons in low-serum and serum-free conditions. *Neuroscience Letters* 708:134353. doi: 10.1016/j.neulet.2019.134353.

Fakhri, S., M. Pesce, A. Patruno, S. Z. Moradi, A. Iranpanah, M. H. Farzaei, and E. Sobarzo-Sánchez. 2020. Attenuation of Nrf2/Keap1/ARE in Alzheimer's disease by plant secondary metabolites: A mechanistic review. *Molecules* 25 (21):4926. doi: 10.3390/molecules25214926.

Fakhri, S., S. Z. Moradi, M. H. Farzaei, and A. Bishayee. 2020. Modulation of dysregulated cancer metabolism by plant secondary metabolites: A mechanistic review. *Seminars in Cancer Biology* doi: 10.1016/j.semcancer.2020.02.007.

Forraz, N., K. Wright, M. Jurga, and C. McGuckin. 2013. Experimental therapies for repair of the central nervous system: Stem cells and tissue engineering. *Journal of Tissue Engineering and Regenerative Medicine* 7 (7):523–36. doi: 10.1002/term.552.

Fu, X., S. Li, S. Zhou, Q. Wu, F. Jin, and J. Shi. 2018. Stimulatory effect of icariin on the proliferation of neural stem cells from rat hippocampus. *BMC Complementary and Alternative Medicine* 18 (1):34 doi: 10.1186/s12906-018-2095-y.

Geldenhuys, W., T. Mbimba, T. Bui, K. Harrison, and V. Sutariya. 2011. Brain-targeted delivery of paclitaxel using glutathione-coated nanoparticles for brain cancers. *Journal of Drug Targeting* 19 (9): 837–45. doi: 10.3109/1061186X.2011.589435.

Geppert, M., M. C. Hohnholt, K. Thiel, S. Nürnberger, I. Grunwald, K. Rezwan, and R. Dringen. 2011. Uptake of dimercaptosuccinate-coated magnetic iron oxide nanoparticles by cultured brain astrocytes. *Nanotechnology* 22 (14):145101. doi: 10.1088/0957-4484/22/14/145101.

Glatzel, M., E. Flechsig, B. Navarro, M. A. Klein, J. C. Paterna, H. Büeler, and A. Aguzzi. 2000. Adenoviral and adeno-associated viral transfer of genes to the peripheral nervous system. *Proceedings of the National Academy of Sciences of the United States of America* 97 (1):442–7. DOI: 10.5167/uzh-1930.

Goes, A. T., C. R. Jesse, M. S. Antunes, F. V. L. Ladd, A. A. L. Ladd, C. Luchese, N. Paroul, and S. P. Boeira. 2018. Protective role of chrysin on 6-hydroxydopamine-induced neurodegeneration a mouse model of Parkinson's disease: Involvement of neuroinflammation and neurotrophins. *Chemico-Biological Interactions* 279:111–20. doi: 10.1016/j.cbi.2017.10.019.

Gomes, B. A. Q., J. P. B. Silva, C. F. R. Romeiro, S. M. dos Santos, C. A. Rodrigues, P. R. Gonçalves, P. R. Sakai, et al. 2018. Neuroprotective mechanisms of resveratrol in Alzheimer's disease: Role of SIRT1. *Oxidative Medicine and Cellular Longevity* 2018: 8152373. doi: 10.1155/2018/8152373.

Haider, S., L. Liaquat, S. Ahmad, Z. Batool, R. A. Siddiqui, S. Tabassum, S. Shahzad, S. Rafiq, and N. Naz. 2020. Naringenin protects AlCl3/D-galactose induced neurotoxicity in rat model of AD via attenuation of acetylcholinesterase levels and inhibition of oxidative stress. *Plos One* 15 (1):e0227631. doi: 10.1371/journal.pone.0227631.

Han, D., H. J. Kim, H. Y. Choi, B. Kim, G. Yang, J. Han, A. A. Dayem, H.-R. Lee, J. H. Kim, et al. K.-M. Lee, 2015. 3,2'-Dihydroxyflavone-treated pluripotent stem cells show enhanced proliferation, pluripotency marker expression, and neuroprotective properties. *Cell Transplant* 24 (8):1511–32. doi: 10.3727/096368914X683511.

He, X., S. Yang, R. Zhang, L. Hou, J. Xu, Y. Hu, R. Xu, H. Wang, and Y. Zhang. 2019. Smilagenin protects dopaminergic neurons in chronic MPTP/probenecid-lesioned Parkinson's disease models. *Frontiers in Cellular Neuroscience* 13:18. doi: 10.3389/fncel.2019.00018.

Heidary Moghaddam, R., Z. Samimi, S. Z. Moradi, P. J. Little, S. Xu, and M. H. Farzaei. 2020. Naringenin and naringin in cardiovascular disease prevention: A preclinical review. *European Journal of Pharmacology* 887:173535. doi: 10.1016/j.ejphar.2020.173535.

Heitman, E., and D. K. Ingram. 2017. Cognitive and neuroprotective effects of chlorogenic acid. *Nutritional Neuroscience* 20 (1):32–39. doi: 10.1179/1476830514Y.0000000146.

Hell, R. C. R., M. M. S. Costa, A. M. Goes, and A. L. Oliveira. 2009. Local injection of BDNF producing mesenchymal stem cells increases neuronal survival and synaptic stability following ventral root avulsion. *Neurobiology of Disease* 33 (2):290–300. doi: 10.1016/j.nbd.2008.10.017.

Hoveizi, E., and S. Ebrahimi-Barough. 2019. Embryonic stem cells differentiated into neuron-like cells using SB431542 small molecule on nanofibrous PLA/CS/Wax scaffold. *Journal of Cellular Physiology* 234 (11):19565–19573. doi: 10.1002/jcp.28554.

Hu, S., P. Maiti, Q. Ma, X. Zuo, M. R. Jones, G. M. Cole, and S. A. Frautschy. 2015. Clinical development of curcumin in neurodegenerative disease. *Expert Review of Neurotherapeutics* 15 (6):629–637. doi: 10.1586/14737175.2015.1044981.

Hu, W., Z. Feng, J. Xu, Z. Jiang, and M. Feng. 2019. Brain-derived neurotrophic factor modified human umbilical cord mesenchymal stem cells-derived cholinergic-like neurons improve spatial learning and memory ability in Alzheimer's disease rats. *Brain Research* 1710: 61–73. doi: 10.1016/j.brainres.2018.12.034.

Islamov, R. R., A. A. Rizvanov, V. Y. Fedotova, A. A. Izmailov, Z. Z. Safiullov, E. E. Garanina, I. I. Salafutdinov, M. E. Sokolov, M. A. Mukhamedyarov, A. Palotás, et al. 2017. A. Palotás. 2017. Tandem delivery of multiple therapeutic genes using umbilical cord blood cells improves symptomatic outcomes in ALS. *Molecular Neurobiology* 54 (6):4756–4763. doi: 10.1007/s12035-016-0017-x.

Jahromi, H. K., A. Farzin, E. Hasanzadeh, S. E. Barough, N. Mahmoodi, M. R. H. Najafabadi, M. S. Farahani, K. Mansoori, S. Shirian, and J. Ai. 2020. Enhanced sciatic nerve regeneration by poly-L-lactic acid/multi-wall carbon nanotube neural guidance conduit containing Schwann cells and curcumin encapsulated chitosan nanoparticles in rat. *Materials Science & Engineering. C, Materials for Biological Applications* 109:110564. doi: 10.1016/j.msec.2019.110564.

Jiang, B., R. F. Shen, J. Bi, X. S. Tian, T. Hinchliffe, and Y. Xia. 2015. Catalpol: A potential therapeutic for neurodegenerative diseases. *Current Medicinal Chemistry* 22 (10):1278–1291. doi: 10.2174/0929867322666150114151720.

Joshi, C. R., V. Labhasetwar, and A. Ghorpade. 2017. Destination brain: The past, present, and future of therapeutic gene delivery. *Journal of Neuroimmune Pharmacology : The Official Journal of the Society on NeuroImmune Pharmacology* 12 (1):51–83. doi: 10.1007/s11481-016-9724-3.

Jurga, M., M. B. Dainiak, A. Sarnowska, A. Jablonska, A. Tripathi, F. M. Plieva, I. N. Savina, L. Strojek, H. Jungvid, et al. A. Kumar, 2011. The performance of laminin-containing cryogel scaffolds in neural tissue regeneration. *Biomaterials* 32 (13):3423–3434. doi: 10.1016/j.biomaterials.2011.01.049.

Katebi, S., A. Esmaeili, K. Ghaedi, and A. Zarrabi. 2019. Superparamagnetic iron oxide nanoparticles combined with NGF

and quercetin promote neuronal branching morphogenesis of PC12 cells. *International Journal of Nanomedicine* 14:2157–2169. doi: 10.2147/IJN.S191878.

Katz, M. G., A. S. Fargnoli, R. D. Williams, and C. R. Bridges. 2013. Gene therapy delivery systems for enhancing viral and nonviral vectors for cardiac diseases: Current concepts and future applications. *Human Gene Therapy* 24 (11):914–927. doi: 10.1089/hum.2013.2517.

Kemp, K., K. Hares, E. Mallam, K. J. Heesom, N. Scolding, and A. Wilkins. 2010. Mesenchymal stem cell-secreted superoxide dismutase promotes cerebellar neuronal survival . *Journal of Neurochemistry* 114 (6):1569–1580. doi: 10.1111/j.1471-4159.2009.06553.x.

Kesh, S., R. R. Kannan, and A. Balakrishnan. 2021. Naringenin alleviates 6-hydroxydopamine induced Parkinsonism in SHSY5Y cells and zebrafish model. *Comparative Biochemistry and Physiology. Toxicology & Pharmacology : CBP* 239:108893. doi: 10.1016/j.cbpc.2020.108893.

Kesh, S., R. R. Kannan, K. Sivaji, and A. Balakrishnan. 2021. Hesperidin downregulates kinases lrrk2 and gsk3β in a 6-OHDA induced Parkinson's disease model. *Neurosci Lett* 740:135426. doi: 10.1016/j.neulet.2020.135426.

Khalatbary, A. R. 2014. Natural polyphenols and spinal cord injury. *Iranian Biomedical Journal* 18 (3):120–doi: 10.609. 1/ibj.1278.2014.

Khan, H., H. Ullah, R. Tundis, T. Belwal, H. P. Devkota, M. Daglia, Z. Cetin, E. I. Saygili, M. d G. Campos, E. Capanoglu, et al. 2020. Dietary flavonoids in the management of Huntington's disease: Mechanism and clinical perspective. *eFood* 1 (1):38–52. doi: 10.2991/efood.k.200203.001.

Kim, J., H. J. Lee, and K. W. Lee. 2010. Naturally occurring phytochemicals for the prevention of Alzheimer's disease. *Journal of Neurochemistry* 112 (6):1415–1430. doi: 10.1111/j.1471-4159.2009.06562.x.

Kim, M. H., S.-H. Kim, and W. M. Yang. 2014. Mechanisms of action of phytochemicals from medicinal herbs in the treatment of Alzheimer's disease. *Planta Medica* 80 (15):1249–1258. doi: 10.1055/s-0034-1383038.

Klejbor, I., E. Stachowiak, D. Bharali, I. Roy, I. Spodnik, J. Morys, E. Bergey, P. Prasad, and M. Stachowiak. 2007. ORMOSIL nanoparticles as a non-viral gene delivery vector for modeling polyglutamine induced brain pathology. *Journal of Neuroscience Methods* 165 (2):230–243. doi: 10.1016/j.jneumeth.2007.06.011.

Kozłowska, H., J. Jabłonka, M. Janowski, M. Jurga, M. Kossut, and K. Domańska-Janik. 2007. Transplantation of a novel human cord blood-derived neural-like stem cell line in a rat model of cortical infarct. *Stem Cells and Development* 16 (3):481–488. doi: 10.1089/scd.2007.9993.

Kubinová, Š. 2020. Biomaterials and magnetic stem cell delivery in the treatment of spinal cord injury. *Neurochemical Research* 45 (1):171–179. doi: 10.1007/s11064-019-02808-2.

Kujawska, M., and J. Jodynis-Liebert. 2018. Polyphenols in Parkinson's disease: A systematic review of in vivo studies. *Nutrients* 10 (5):642. doi: 10.3390/nu10050642.

Lagoa, R., C. Lopez-Sanchez, A. Samhan-Arias, C. M. Ganan, V. Garcia-Martinez, and C. Gutiérrez-Merino. 2009. Neuroprotective effect of kaempferol in the 3-nitropropionic acid model of Huntington's disease. *Free Radical Research* 43:71.

Lee, D.-C., J.-H. Chen, T.-Y. Hsu, L.-H. Chang, H. Chang, Y.-H. Chi, and I.-M. Chiu. 2017. Neural stem cells promote nerve regeneration through IL12-induced Schwann cell differentiation. *Molecular and Cellular Neurosciences* 79:1–11. doi: 10.1016/j.mcn.2016.11.007.

Lee, S.-T., K. Chu, K.-H. Jung, H.-J. Yoon, D. Jeon, K.-M. Kang, K.-H. Park, E.-K. Bae, M. Kim, S. K. Lee, et al. 2010. MicroRNAs induced during ischemic preconditioning. *Stroke* 41 (8):1646–1651. doi: 10.1161/STROKEAHA.110.579649.

Li, C., J. Zhang, P.-Q. Zhu, C-h Ma, L-h Yuan, J. Lu, Z.-Z. Luo, and G.-H. Xu. 2016. Intrathecal administration of flavopiridol promotes regeneration in experimental model of spinal cord injury. *Turkish Neurosurgery* 26 (6):922–929. doi: 10.5137/1019-5149.JTN.13745-15.2.

Li, J., Y. Liu, L. Wang, Z. Gu, Z. Huan, H. Fu, and Q. Liu. 2020. Hesperetin protects SH-SY5Y cells against 6-hydroxydopamine-induced neurotoxicity via activation of NRF2/ARE signaling pathways. *Tropical Journal of Pharmaceutical Research* 19 (6):1197–1201. doi: 10.4314/tjpr.v19i6.12.

Li, X., J. Zhang, H. Rong, X. Zhang, and M. Dong. 2020. Ferulic acid ameliorates MPP+/MPTP-induced oxidative stress via ERK1/2-dependent Nrf2 activation: translational implications for Parkinson disease treatment. *Molecular Neurobiology* 57 (7):2981–2995. doi: 10.1007/s12035-020-01934-1.

Li, Y., Q. Tian, Z. Li, M. Dang, Y. Lin, and X. Hou. 2019. Activation of Nrf2 signaling by sitagliptin and quercetin combination against β-amyloid induced Alzheimer's disease in rats. *Drug Development Research* 80 (6):837–845. doi: 10.1002/ddr.21567.

Lim, D. A., A. D. Tramontin, J. M. Trevejo, D. G. Herrera, J. M. García-Verdugo, and A. Alvarez-Buylla. 2000. Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. *Neuron* 28 (3):713–726. doi: 10.1016/S0896-6273(00)00148-3.

Limongi, T., A. Rocchi, F. Cesca, H. Tan, E. Miele, A. Giugni, M. Orlando, M. P. Donnorso, G. Perozziello, et al. F. Benfenati, 2018. Delivery of brain-derived neurotrophic factor by 3D biocompatible polymeric scaffolds for neural tissue engineering and neuronal regeneration. *Molecular Neurobiology* 55 (12):8788–8798. doi: 10.1007/s12035-018-1022-z.

Lin, J., X. Huo and X. Liu. 2017. "mTOR signaling pathway": A potential target of curcumin in the treatment of spinal cord injury. *BioMed research international* 2017. doi: 10.1155/2017/1634801.

Liu, S., B. Sandner, T. Schackel, L. Nicholson, A. Chtarto, L. Tenenbaum, R. Puttagunta, R. Müller, N. Weidner, and A. Blesch. 2017. Regulated viral BDNF delivery in combination with Schwann cells promotes axonal regeneration through capillary alginate hydrogels after spinal cord injury. *Acta Biomaterialia* 60:167–180. doi: 10.1016/j.actbio.2017.07.024.

Longo, F. M., T. Yang, Y. Xie, and S. M. Massa. 2006. Small molecule approaches for promoting neurogenesis. *Current Alzheimer Research* 3 (1):5–10. doi: 10.2174/156720506775697089.

Lopes, C. D., N. P. Gonçalves, C. P. Gomes, M. J. Saraiva, and A. P. Pêgo. 2017. BDNF gene delivery mediated by neuron-targeted nanoparticles is neuroprotective in peripheral nerve injury. *Biomaterials* 121:83–96. doi: 10.1016/j.biomaterials.2016.12.025.

Luo, L., Y. He, X. Wang, B. Key, B. H. Lee, H. Li, and Q. Ye. 2018. Potential roles of dental pulp stem cells in neural regeneration and repair. *Stem Cells International* 2018:1731289–15. doi: 10.15/2018/1731289.

Luther, E. M., Y. Koehler, J. Diendorf, M. Epple, and R. Dringen. 2011. Accumulation of silver nanoparticles by cultured primary brain astrocytes. *Nanotechnology* 22 (37):375101. doi: 10.1088/0957-4484/22/37/375101.

Ma, F., T. Zhu, F. Xu, Z. Wang, Y. Zheng, Q. Tang, L. Chen, Y. Shen, and J. Zhu. 2017. Neural stem/progenitor cells on collagen with anchored basic fibroblast growth factor as potential natural nerve conduits for facial nerve regeneration. *Acta Biomaterialia* 50:188–197. doi: 10.1016/j.actbio.2016.11.064.

Ma, J., H. Yu, J. Liu, Y. Chen, Q. Wang, and L. Xiang. 2016. Curcumin promotes nerve regeneration and functional recovery after sciatic nerve crush injury in diabetic rats. *Neuroscience Letters* 610:139–143. doi: 10.1016/j.neulet.2015.11.005.

Ma, W., W. Fitzgerald, Q.-Y. Liu, T. O'shaughnessy, D. Maric, H. Lin, D. Alkon, and J. Barker. 2004. CNS stem and progenitor cell differentiation into functional neuronal circuits in three-dimensional collagen gels. *Experimental Neurology* 190 (2):276–288. doi: 10.1016/j.expneurol.2003.10.016.

Mahar, M., and V. Cavalli. 2018. Intrinsic mechanisms of neuronal axon regeneration. *Nature Reviews. Neuroscience* 19 (6):323–337. doi: 10.1038/s41583-018-0001-8.

Mao, A. S., and D. J. Mooney. 2015. Regenerative medicine: Current therapies and future directions. *Proceedings of the National Academy of Sciences of the United States of America* 112 (47):14452–14459. doi: 10.1073/pnas.1508520112.

Masgutov, R., G. Masgutova, A. Mullakhmetova, M. Zhuravleva, A. Shulman, A. Rogozhin, V. Syromiatnikova, D. Andreeva, A. Zeinalova, and K. Idrisova. 2019. Adipose-derived mesenchymal

stem cells applied in fibrin glue stimulate peripheral nerve regeneration. *Frontiers in Medicine* 6:68. doi: 10.3389/fmed.2019.00068.

Maxson, S., E. A. Lopez, D. Yoo, A. Danilkovitch-Miagkova, and M. A. LeRoux. 2012. Concise review: role of mesenchymal stem cells in wound repair. *Stem Cells Translational Medicine* 1 (2):142–149. doi: 10.5966/sctm.2011-0018.

McMahan, C. A., S. S. Gidding, G. T. Malcom, R. E. Tracy, J. P. Strong, and H. C. McGill. 2006. Pathobiological determinants of atherosclerosis in youth risk scores are associated with early and advanced atherosclerosis. *Pediatrics* 118 (4):1447–1455. doi: 10.1542/peds.2006-0970.

Miao, G., H. Zhao, K. Guo, J. Cheng, S. Zhang, X. Zhang, Z. Cai, H. Miao, and Y. Shang. 2014. Mechanisms underlying attenuation of apoptosis of cortical neurons in the hypoxic brain by flavonoids from the stems and leaves of Scutellaria baicalensis Georgi. *Neural Regeneration Research* 9 (17):1592–doi: 10.4103/1673-5374.14178. 4.

Monfared, A., A. Ghaee, and S. Ebrahimi-Barough. 2018. Fabrication of tannic acid/poly(N-vinylpyrrolidone) layer-by-layer coating on Mg-based metallic glass for nerve tissue regeneration application. *Colloids and Surfaces. B, Biointerfaces* 170:617–626. doi: 10.1016/j.colsurfb.2018.06.060.

Moradi, S. Z., S. Momtaz, Z. Bayrami, M. H. Farzaei, and M. Abdollahi. 2020. Nanoformulations of herbal extracts in treatment of neurodegenerative disorders. *Frontiers in Bioengineering and Biotechnology* 8:238. doi: 10.3389/fbioe.2020.00238.

Nabavi, S. F., K. P. Devi, D. S. Malar, A. Sureda, M. Daglia, and S. M. Nabavi. 2015. Ferulic acid and Alzheimer's disease: Promises and pitfalls. *Mini Reviews in Medicinal Chemistry* 15 (9):776–788. doi: 10.2174/1389557515666150522102545.

Naoi, M., K. Inaba-Hasegawa, M. Shamoto-Nagai, and W. Maruyama. 2017. Neurotrophic function of phytochemicals for neuroprotection in aging and neurodegenerative disorders: Modulation of intracellular signaling and gene expression. *Journal of Neural Transmission (Vienna, Austria : 1996)* 124 (12):1515–1527. doi: 10.1007/s00702-017-1797-5.

Naoi, M., M. Shamoto-Nagai, and W. Maruyama. 2019. Neuroprotection of multifunctional phytochemicals as novel therapeutic strategy for neurodegenerative disorders: Antiapoptotic and antiamyloidogenic activities by modulation of cellular signal pathways. *Future Neurology* 14 (1):FNL9. doi: 10.2217/fnl-2018-0028.

Nasrallah, H. A., T. Hopkins, and S. K. Pixley. 2010. Differential effects of antipsychotic and antidepressant drugs on neurogenic regions in rats. *Brain Research* 1354:23–29. doi: 10.1016/j.brainres.2010.07.075.

Nguyen, L. H., M. Gao, J. Lin, W. Wu, J. Wang, and S. Y. Chew. 2017. Three-dimensional aligned nanofibers-hydrogel scaffold for controlled non-viral drug/gene delivery to direct axon regeneration in spinal cord injury treatment. *Scientific Reports* 7:42212. doi: 10.1038/srep42212.

Nouri, Z., S. Fakhri, F. F. El-Senduny, N. Sanadgol, G. E. Abd-ElGhani, M. H. Farzaei, and J.-T. Chen. 2019. On the neuroprotective effects of naringenin: pharmacological targets, signaling pathways, molecular mechanisms, and clinical perspective. *Biomolecules* 9 (11):690. doi: 10.3390/biom9110690.

Ogunsuyi, O. B., G. Oboh, O. O. Oluokun, A. O. Ademiluyi, and O. O. Ogunruku. 2020. Gallic acid protects against neurochemical alterations in transgenic Drosophila model of Alzheimer's disease. *Advances in Traditional Medicine* 20 (1):89–98. doi: 10.1007/s13596-019-00393-x.

Olajide, O. A., A. Kumar, R. Velagapudi, U. P. Okorji, and B. L. Fiebich. 2014. Punicalagin inhibits neuroinflammation in LPS-activated rat primary microglia. *Molecular Nutrition & Food Research* 58 (9):1843–1851. doi: 10.1002/mnfr.201400163.

Oliveira, M. A., L. Heimfarth, F. R. S. Passos, R. Miguel-dos-Santos, M. R. Mingori, J. C. F. Moreira, S. S. Lauton, R. S. S. Barreto, A. A. S. Araújo, A. P. Oliveira, et al. 2020. Naringenin complexed with hydroxypropyl-β-cyclodextrin improves the sciatic nerve regeneration through inhibition of p75NTR and JNK pathway. *Life Sci* 241:117102. doi: 10.1016/j.lfs.2019.117102.

Önger, M. E., B. Delibaş, A. P. Türkmen, E. Erener, B. Z. Altunkaynak, and S. Kaplan. 2017. The role of growth factors in nerve regeneration. *Drug Discoveries & Therapeutics* 10 (6):285–291. doi: 10.5582/ddt.2016.01058.

Park, K. I., Y. D. Teng, and E. Y. Snyder. 2002. The injured brain interacts reciprocally with neural stem cells supported by scaffolds to reconstitute lost tissue. *Nature Biotechnology* 20 (11):1111–doi: 10.1038/nbt7. 51.

Patil, S. P., P. D. Jain, J. S. Sancheti, P. J. Ghumatkar, R. Tambe, and S. Sathaye. 2014. Neuroprotective and neurotrophic effects of Apigenin and Luteolin in MPTP induced parkinsonism in mice. *Neuropharmacology* 86:192–202. doi: 10.1016/j.neuropharm.2014.07.012.

Pêgo, A. P., H. Oliveira, and P. M. Moreno. 2013. Biomaterial-based vectors for targeted delivery of nucleic acids to the nervous system. In *Drug delivery systems: Advanced technologies potentially applicable in personalised treatment*, ed. Jorge Coelho, 185–224. Netherlands: Springer. doi: 10.1007/978-94-007-6010-3_7.

Pilakka-Kanthikeel, S., V. S. R. Atluri, V. Sagar, S. K. Saxena, and M. Nair. 2013. Targeted brain derived neurotropic factors (BDNF) delivery across the blood-brain barrier for neuro-protection using magnetic nano carriers: An in-vitro study. *PloS One* 8 (4):e62241. doi: 10.1371/journal.pone.0062241.

Pirasteh, A., A. Naseri, M. Farhadi, J. Fahanik Babaee, and L. Elyasi. 2020. Beta-amyloid formation, memory and learning decline following long-term ovariectomy are inhibited by systemic administration of apigenin and β-estradiol. *Basic and Clinical Neuroscience*.doi: 10.32598/bcn.12.3.2634.1.

Prema, A., U. Janakiraman, T. Manivasagam, and A. J. Thenmozhi. 2015. Neuroprotective effect of lycopene against MPTP induced experimental Parkinson's disease in mice. *Neuroscience Letters* 599:12–19. doi: 10.1016/j.neulet.2015.05.024.

Qian, Y., T. Guan, M. Huang, L. Cao, Y. Li, H. Cheng, H. Jin, and D. Yu. 2012. Neuroprotection by the soy isoflavone, genistein, via inhibition of mitochondria-dependent apoptosis pathways and reactive oxygen induced-NF-κB activation in a cerebral ischemia mouse model . *Neurochemistry International* 60 (8):759–767. doi: 10.1016/j.neuint.2012.03.011.

Ramezani, M., N. Darbandi, F. Khodagholi, and A. Hashemi. 2016. Myricetin protects hippocampal CA3 pyramidal neurons and improves learning and memory impairments in rats with Alzheimer's disease. *Neural Regeneration Research* 11 (12):1976–1980. doi: 10.4103/1673-5374.197141.

Rehman, M. U., A. F. Wali, A. Ahmad, S. Shakeel, S. Rasool, R. Ali, S. M. Rashid, H. Madkhali, M. A. Ganaie, and R. Khan. 2019. Neuroprotective strategies for neurological disorders by natural products: An update. *Current Neuropharmacology* 17 (3):247–267. doi: 10.2174/1570159x16666180911124605.

Roghani, M., A. Niknam, M.-R. Jalali-Nadoushan, Z. Kiasalari, M. Khalili, and T. Baluchnejadmojarad. 2010. Oral pelargonidin exerts dose-dependent neuroprotection in 6-hydroxydopamine rat model of hemi-parkinsonism. *Brain Research Bulletin* 82 (5–6):279–283. doi: 10.1016/j.brainresbull.2010.06.004.

Ruppert, K. A., S. D. Olson, and C. S. Cox. 2019. Chapter 13 - Spinal cord injury. In *A roadmap to non-hematopoietic stem cell-based therapeutics*, ed. X.-D. Chen, 321–43. Cambridge: Academic Press.

Samadian, H., A. Vaez, A. Ehterami, M. Salehi, S. Farzamfar, H. Sahrapeyma, and P. Norouzi. 2019. Sciatic nerve regeneration by using collagen type I hydrogel containing naringin. *Journal of Materials Science: Materials in Medicine* 30 (9):107. doi: 10.1007/s10856-019-6309-8.

Samavarchi-Tehrani, P., A. Golipour, L. David, H-k Sung, T. A. Beyer, A. Datti, K. Woltjen, A. Nagy, and J. L. Wrana. 2010. Functional genomics reveals a BMP-driven mesenchymal-to-epithelial transition in the initiation of somatic cell reprogramming. *Cell Stem Cell* 7 (1):64–77. doi: 10.1016/j.stem.2010.04.015.

Sasaki, M., C. Radtke, A. M. Tan, P. Zhao, H. Hamada, K. Houkin, O. Honmou, and J. D. Kocsis. 2009. BDNF-hypersecreting human mesenchymal stem cells promote functional recovery, axonal sprouting, and protection of corticospinal neurons after spinal cord injury. *The Journal of Neuroscience : The Official Journal of the Society for*

Neuroscience 29 (47):14932–14941. doi: 10.1523/JNEUROSCI.2769-09.2009.

Scott, J. 2004. Pathophysiology and biochemistry of cardiovascular disease. *Current Opinion in Genetics & Development* 14 (3):271–279. doi: 10.1016/j.gde.2004.04.012.

Shah, L., S. Yadav, and M. Amiji. 2013. Nanotechnology for CNS delivery of bio-therapeutic agents. *Drug Delivery and Translational Research* 3 (4):336–351. doi: 10.1007/s13346-013-0133-3.

Shamsher, E., R. Sulaimankutty, K. Dine, V. Luong, B. Davis, K. Willett, S. Somavarapu, M. F. Cordeiro, and K. S. Shindler. 2020. Intranasal delivery of resveratrol nanoparticles reduces retinal ganglion cell loss in a model of multiple sclerosis. *Investigative Ophthalmology & Visual Science* 61 (7):2476–2476.

Shariati, M., V. Shaygannejad, F. Abbasirad, F. Hosseininasab, M. Kazemi, O. Mirmosayyeb, and N. Esmaeil. 2019. Silymarin restores regulatory T cells (tregs) function in multiple sclerosis (MS) patients in vitro. *Inflammation* 42 (4):1203–1214. doi: 10.1007/s10753-019-00980-9.

Sharma, S., K. Raj, and S. Singh. 2020. Neuroprotective effect of quercetin in combination with piperine against rotenone- and iron supplement-induced Parkinson's disease in experimental rats. *Neurotoxicity Research* 37 (1):198–209. doi: 10.1007/s12640-019-00120-z.

Singh, N. A., A. K. A. Mandal, and Z. A. Khan. 2016. Potential neuroprotective properties of epigallocatechin-3-gallate (EGCG). *Nutrition Journal* 15 (1):60–60. doi: 10.1186/s12937-016-0179-4.

Stabenfeldt, S. E., A. J. García, and M. C. LaPlaca. 2006. Thermoreversible laminin-functionalized hydrogel for neural tissue engineering. *Journal of Biomedical Materials Research. Part A* 77 (4):718–725. doi: 10.1002/jbm.a.30638.

Steward, M. M., A. Sridhar, and J. S. Meyer. 2012. Neural regeneration. In *New perspectives in regeneration*, ed. E. Heber-Katz and D. L. Stocum, 163–91. Netherlands: Springer.

Strathearn, K. E., G. G. Yousef, M. H. Grace, S. L. Roy, M. A. Tambe, M. G. Ferruzzi, Q.-L. Wu, J. E. Simon, M. A. Lila, and J.-C. Rochet. 2014. Neuroprotective effects of anthocyanin- and proanthocyanidin-rich extracts in cellular models of Parkinson′s disease. *Brain Research* 1555:60–77. doi: 10.1016/j.brainres.2014.01.047.

Su, X., A. P. Kells, E. J. Huang, H. S. Lee, P. Hadaczek, J. Beyer, J. Bringas, P. Pivirotto, J. Penticuff, et al. J. Eberling, 2009. Safety evaluation of AAV2-GDNF gene transfer into the dopaminergic nigrostriatal pathway in aged and parkinsonian rhesus monkeys. *Human Gene Therapy* 20 (12):1627–1640. doi: 10.1089/hum.2009.103.

Szwajgier, D., K. Borowiec, and K. Pustelniak. 2017. The neuroprotective effects of phenolic acids: Molecular mechanism of action. *Nutrients* 9 (5):477. doi: 10.3390/nu9050477.

Tan, J.-K Y., D. L. Sellers, B. Pham, S. H. Pun, and P. J. Horner. 2016. Non-viral nucleic acid delivery strategies to the central nervous system. *Frontiers in Molecular Neuroscience* 9:108. doi: 10.3389/fnmol.2016.00108.

Taylor, J. P., R. H. Brown, Jr, and D. W. Cleveland. 2016. Decoding ALS: From genes to mechanism. *Nature* 539 (7628):197–206. doi: 10.1038/nature20413.

Tosi, G., B. Bortot, B. Ruozi, D. Dolcetta, M. A. Vandelli, F. Forni, and G. Severini. 2013. Potential use of polymeric nanoparticles for drug delivery across the blood-brain barrier. *Current Medicinal Chemistry* 20 (17):2212–2225. doi: 10.2174/0929867311320170006.

Towne, C., M. Pertin, A. T. Beggah, P. Aebischer, and I. Decosterd. 2009. Recombinant adeno-associated virus serotype 6 (rAAV2/6)-mediated gene transfer to nociceptive neurons through different routes of delivery. *Molecular Pain* 5 (1):1744-8069-5-52. doi: 10.1186/1744-8069-5-52.

Van Kampen, J. M., and D. G. Kay. 2017. Progranulin gene delivery reduces plaque burden and synaptic atrophy in a mouse model of Alzheimer's disease. *PloS One* 12 (8):e0182896. doi: 10.1371/journal.pone.0182896.

Wada, A. 2009. Lithium and neuropsychiatric therapeutics: Neuroplasticity via glycogen synthase kinase-3β, β-catenin, and neurotrophin cascades. *Journal of Pharmacological Sciences* 110 (1):14–28. doi: 10.1254/jphs.09R02CR.

Wang, D., L. Zhong, M. A. Nahid, and G. Gao. 2014. The potential of adeno-associated viral vectors for gene delivery to muscle tissue. *Expert Opinion on Drug Delivery* 11 (3):345–364. doi: 10.1517/17425247.2014.871258.

Weir, M. R. 2014. In the clinic: Hypertension. *Annals of Internal Medicine* 161 (11):ITC1–ITC1. doi: 10.7326/AITC201905070.

Wion, D., D. MacGrogan, I. Neveu, F. Jehan, R. Houlgatte, and P. Brachet. 1991. 1,25-Dihydroxyvitamin D3 is a potent inducer of nerve growth factor synthesis . *Journal of Neuroscience Research* 28 (1):110–114. doi: 10.1002/jnr.490280111.

Wong, H. L., X. Y. Wu, and R. Bendayan. 2012. Nanotechnological advances for the delivery of CNS therapeutics. *Advanced Drug Delivery Reviews* 64 (7):686–700. doi: 10.1016/j.addr.2011.10.007.

Wright, D. L., C. R. Whitehead, E. H. Sessions, I. Ghiviriga, and D. A. Frey. 1999. Studies on inducers of nerve growth factor: Synthesis of the cyathin core. *Organic Letters* 1 (10):1535–1538. doi: 10.1021/ol991032y.

Wyss-Coray, T. 2016. Ageing, neurodegeneration and brain rejuvenation. *Nature* 539 (7628):180–186. doi: 10.1038/nature20411.

Xu, K., F. Liu, W. Xu, J. Liu, S. Chen, and G. Wu. 2019. Transplanting GABAergic neurons differentiated from neural stem cells into hippocampus inhibits seizures and epileptiform discharges in pilocarpine-induced temporal lobe epilepsy model. *World Neurosurgery* 128:e1–e11. doi: 10.1016/j.wneu.2019.01.245.

Yang, J., S. Song, J. Li, and T. Liang. 2014. Neuroprotective effect of curcumin on hippocampal injury in 6-OHDA-induced Parkinson's disease rat. *Pathology - Research and Practice* 210 (6):357–362. doi: 10.1016/j.prp.2014.02.005.

Yiu, G., and Z. He. 2006. Glial inhibition of CNS axon regeneration. *Nature Reviews. Neuroscience* 7 (8):617–627. doi: 10.1038/nrn1956.

Yu, g., G. Fischer, G. Jia, J. Reiser, F. Park, and Q. H. Hogan. 2011. Lentiviral gene transfer into the dorsal root ganglion of adult rats. *Molecular Pain* 7:63–8069. 1747-1763. doi: 10.1186/1744-8069-7-63.

Zhang, N., and X. Wen. 2009. Neural tissue engineering and regenerative medicine. In *Fundamentals of tissue engineering and regenerative medicine*, ed. Ulrich MeyerJörg, Handschel Hans, Peter Wiesmann, and Thomas Meyer, 271–88. Netherlands: Springer.

Zhang, Y., L. Yin, N. Zheng, L. Zhang, J. Liu, W. Liang, and Q. Wang. 2017. Icariin enhances remyelination process after acute demyelination induced by cuprizone exposure. *Brain Research Bulletin* 130:180–187. doi: 10.1016/j.brainresbull.2017.01.025.

Zheng, Z. V., C. Y. Cheung, H. Lyu, H. Y. Chan, Y. Li, Z. X. Bian, K. K. Wang, and W. S. Poon. 2019. Baicalein enhances the effect of low dose Levodopa on the gait deficits and protects dopaminergic neurons in experimental Parkinsonism. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia* 64:242–251. doi: 10.1016/j.jocn.2019.02.005.

Zhou, W.-B., Z.-N. Miao, B. Zhang, W. Long, F.-X. Zheng, J. Kong, and B. Yu. 2019. Luteolin induces hippocampal neurogenesis in the Ts65Dn mouse model of Down syndrome. *Neural Regeneration Research* 14 (4):613–620. doi: 10.4103/1673-5374.248519.