Four main therapeutic keys for Parkinson’s disease: A mini review

Daniel Hernandez-Baltazar 1*, Rasajna Nadella 2, Laura Mireya Zavala-Flores 3, Christian de Jesús Rosas-Jarquin 4, María de Jesús Rovirosa-Hernandez 4, Arnulfo Villanueva-Olivo 5

1 CONACYT-Instituto de Neuroetologia, Universidad Veracruzana, Xalapa, Veracruz, Mexico
2 IIIT Srikakulam, Rajiv Gandhi University of Knowledge Technologies (RGUKT); International collaboration ID: 1840; India
3 Centro de Investigación Biomédica del Noreste. IMSS. Monterrey, Nuevo Leon. Mexico
4 Instituto de Neuroetologia, Universidad Veracruzana. Xalapa, Veracruz, Mexico
5 Facultad de Medicina. Universidad Autonoma de Nuevo Leon. Monterrey, Nuevo Leon, Mexico

A R T I C L E  I N F O

Article type: Mini review article

Article history:
Received: Jul 24, 2018
Accepted: Jan 8, 2019

Keywords: Cell death
Dopaminergic neurons
Inflammation
Survival
Therapeutics

A B S T R A C T

Objective(s): Parkinson’s disease (PD) is characterized by motor and cognitive dysfunctions. The progressive degeneration of dopamine-producing neurons that are present in the substantia nigra pars compacta (SNpc) has been the main focus of study and PD therapies since ages.

Materials and Methods: In this manuscript, a systematic revision of experimental and clinical evidence of PD-associated cell process was conducted.

Results: Classically, the damage in the dopaminergic neuronal circuits of SNpc is favored by reactive oxidative/nitrosative stress, leading to cell death. Interestingly, the therapy for PD has only focused on avoiding the symptom progression but not in finding a complete reversion of the disease. Recent evidence suggests that the renin-angiotensin system imbalance and neuroinflammation are the main keys in the progression of experimental PD.

Conclusion: The progression of neurodegeneration in SNpc is due to the complex interaction of multiple processes. In this review, we analyzed the main contribution of four cellular processes and discussed in the perspective of novel experimental approaches.

Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disease worldwide, with high annual costs of treatment (1). This progressive neurological disorder is characterized by gradual progression of neuronal damage in various motor and non-motor circuits (2). Currently, PD affects the adult population (>65 years) and even young people (3). PD affects a wide variety of nuclei in the central nervous system (CNS), including the dorsal motor nucleus of the vagus, raphe nuclei, locus coeruleus, pontine peduncle nucleus, retrolubar nucleus, parabrachial nucleus, the ventral tegmental area, substantia nigra pars compacta (SNpc), and substantia nigra pars reticulata (SNpr) (4). The degenerative process develops mainly in the dopaminergic neurons (DN), which exhibit native susceptibility to degeneration (5). In humans and the experimental models of PD, the loss of dopaminergic neurons from the SNpc drastically reduces the striatal dopamine concentration (6, 7) promoting motor imbalance, the main characteristic feature that is explored in clinical treatments.

Conventional therapies for Parkinson’s disease

Since years ago, the most commonly used PD treatments has included surgical methods like-pallidotomy or deep brain stimulation (DBS) and pharmacological therapy for each and every PD symptom (B-10). DBS is good at reducing the neuronal loss, avoiding motor fluctuations and preventing damage to the adjacent neurons. On the other hand, DBS is expensive, may cause akinesia and dyskinesia and presence of high risk due to surgical intervention.

Pharmacological therapy with levodopa (11-13) is specific to the dopaminergic system and decreases motor symptoms; however, it promotes hypersensibility of receptors and overdoses induce dyskinesia. On the other hand, adenosine A2A (14) decreases dyskinesia, inducing low neuroinflammation, but sleep disorders and anxiety are reported. Oral administration of monoamine oxidase type B (MAO-B) inhibitors (15-17) is specific to the dopaminergic system and decreases free radicals and increases the levels of trophic factors in neurons. However it is not specific for the dopaminergic system, and long-term use may lead to hypertensive crisis, cerebrovascular accident, and weight gain. The oral or subcutaneous use of dopamine agonists (18, 19) lead to neuroprotection of the nigrostriatal pathway, but hallucinations, edema, and addiction have been reported as adverse effects.

The effectiveness of both pharmacological and gene therapy treatments depends on the level of brain neurodegeneration, and thus, determination of cellular processes at neurodegeneration is the key to improving the treatment efficacy.

*Corresponding author: Daniel Hernandez-Baltazar. Avenida Dr Luis Castelazo S/N. Km. 3.5. Carretera Federal. Col. Industrial Animas. C. P. 91190. Xalapa, Veracruz, Mexico. +52 228 841-89-00 ext. 13619; Email: danielhernandez@uv.mx
Cellular process associated with degeneration in substantia nigra pars compacta

Oxidative stress

Many scientific reports have demonstrated that oxidative stress produces neurodegeneration (20, 21). In normal conditions of the cell, the reactive oxygen (ROS) and nitrogen (RNS) species act as secondary messengers in cell processes, however, an excess of ROS is responsible for cell degeneration (22, 23). Dopaminergic neurons of SNpc are more susceptible to oxidative/nitrosative damage because they have low levels of glutathione peroxidase and vitamin E; as well as high levels of free iron (pro-oxidant), monoamine oxidase, and neuromelanin (5, 24, 25), for this the intracellular accumulation of ROS can induce mitochondrial respiratory chain blocking, increase of glutamate, and stimulation of NMDA receptors (4) to finally produce excitotoxicity (26) and cell death by necrosis and apoptosis (27). Additionally, in PD animal models has been shown that complex axonal arborization, elevated mitochondrial bioenergetics (28-30), and selective vulnerability of neuronal populations (31) could contribute to the speed of neurodegeneration. Reverting the damage might be possible by controlling or modifying the ROS/RNS, which is one possible key for PD therapy.

Cell death

PD is characterized by programmed cell death, which is a homeostatic regulatory function of cells that requires energy in the form of ATP. This programmed cell death is of three types: type I cell death or apoptosis, type II cell death or autophagic cell death, and type III cell death or cytoplasmic cell death (32). In all three types the imbalance of mitochondrial bioenergetics favors DN degeneration in PD (33), which results in alterations of genes such as alpha-synuclein, SNCA, PINK 1, DJ-1, LRRK2, ATP13A2, PLA2G6, FBX07, and VPS35 (34-36). In experimental studies three cell death types associated with DN damage have been identified, which include mitophagy (37, 38), autophagy (39, 40), and caspase-3-related apoptosis. Cellular stress can induce activation of caspase-3 by extrinsic and intrinsic pathways of apoptosis in the SNpc (41, 42) and favor the expression of pro-apoptotic genes such as Bax and Bad similar to ischemic stroke (43). In experimental models, it has linked the role of caspase-3, glycogen synthase kinase 3-beta (GSK3β) and protein kinase Cβ (PKCβ) as a switch between neurodegeneration and regeneration (42, 44, 45). As apoptosis is the most reported, development of new drugs that could modulate the pathways and direct towards neuronal survival would be one possible key for PD therapy.

Neuroinflammation

As per Grunewald et al. (37), most studies exhibit the neurons as protagonists in PD. However, the participation of other brain populations gives evidence of a complex phenomenon. The neuroinflammation in PD is also characterized by the presence of increased number of activated microglia and astrocytes around the degenerated neurons (46).

Under high oxidative stress conditions, microglial cells release reactive oxygen / nitrogen species (H$_2$O$_2$, -NO$_3$) and pro-inflammatory cytokines (IL-1β, IL-6 and TNFα) (47), which serve as signals for the recruitment of more microglial cells, causing imbalance in both neuronal growth and in the release of neurotrophic factors (47). The microglia populations present in damaged SNpc can correspond to two opposite types of microglia, cytotoxic (M1 type) and neuroprotective (M2 type) (48). In experimental models of PD, the cytotoxic microglia (M1) have been evidenced during the progress of DN degeneration in SNpc as a consequence of ROS increase, Lewy bodies (LB) formation, and cell death; stimuli as aggregated alpha-synuclein in Lewy bodies may activate M1-microglia and favor the release of pro-inflammatory responses.

In human post-mortem samples, the alpha-synuclein protein, the main component of LB, has been found in the pre-synaptic terminals of neurons and axons (49). Based on the presence of LB three phases of degenerative damage have been described: 1) LB positive (LB+) neurons without microglia involvement, 2) LB+ neurons with recruited microglia, and 3) LB+ neurons with activated astrocytes. For treating PD the knowledge of the stage-specific switching of M1/M2 phenotypes could be used in therapeutic approaches (48, 50-52).

On the other hand, after neuronal injury, mature astrocytes proliferate and acquire stem cell properties (53-55) promoting neuronal regeneration by synthesizing neurotrophic factors such as glia-derived neurotrophic factor (GDNF) (56) and cerebral dopamine neurotrophic factor (CDNF) (57), and recovery of brain blood irrigation via angiotensin type 2 (AT2) (58), the most important effector peptide of the renin-angiotensin system (RAS) (59). Finding a drug that could induce any of the glia to produce more neurotrophic factor or to release anti-inflammatory cytokine production will be a possible key for PD therapy.

Renin-angiotensin 2 system (RAS)

The actions of angiotensin 2 (AT2) are mediated by AT1 and AT2-receptors. AT2 increases the differentiation of precursor cells in dopaminergic neurons via activation of AT2-receptor (60, 61). It has also been observed that activation of AT2-receptor may inhibit the production of NADPH oxidase (62), supporting the neuroprotective effect due to RAS. However, the overproduction of AT2 could induce inflammation by promoting oxidative stress derived from NADPH via AT1-receptors (63, 64), which proposes the amplifying effect of AT2 during dopaminergic degeneration (6, 62). Interestingly, in PD patients increased local and peripheral levels of angiotensin are associated with motor and non-motor symptoms (59, 65-69).

In experimental models of PD, the high levels of AT2 and ROS induce increased neuron/glial type 2 (NG2) populations (70, 71), precursor cells of immature neurons, oligodendrocytes, Bergmann glia, microglia, and astrocytes depending on the stimulus (46, 57, 72-74). NG2 cells respond very quickly after injury by upregulating the expression of contains chondroitin sulfate proteoglycan 4 (CSPG4) on their surface and exhibiting migration and proliferative potential (75-78). Actually, there are no clinical trials evaluating the effect of RAS. Developing or finding a drug that could stimulate...
the conversion of NG2 cells to immature neurons would be another possible key for PD therapy.

Novel experimental approaches
As oxidative stress, cell death, neuroinflammation, and RAS system play crucial roles in the degeneration process, new drugs that could control or completely revert stress factors might act as keys for PD therapy. The Figure 1 shows the interaction of cellular processes above-revised, the new experimental approaches are focused on some of these hot points. Alternative experimental therapies such as targeted gene delivery, specific drugs, and plant-based antioxidant approaches are revised. In animal models, focusing the regulation of cell death, the use of GSK3 inhibitors and the upregulation of chaperone-mediated autophagy (CMA) by retinoic acid derivatives and micro RNAs (miRNAs) have yielded discrete results. The disadvantages of GSK3 inhibitors include the inhibition of kinase leading to severe side-effects due to its multiple cellular targets; while the upregulation of CMA could be promising by the use of safety administration route. Coupled with this, the use of melatonin as a neuroprotective agent continues to be evaluated. In the field of control of ROS and neuroinflammation, pretreatment with synthetic neuromodulators, curcumin, or other plants derivatives could represent benefits, but further studies on bioavailability, dosage, and biosecurity will be required.

In clinical trials, the capability of GDNF and neurturin to rescue dopaminergic neurons in SNpc has been tested, the results are promising, but due to the lack of safety and specificity, they did not turn out to be a therapeutic medicine. In general, targeted gene delivery using viral vectors shows selectivity for dopaminergic neurons, averts neuronal loss, and local increase in the levels of neurotrophic factors that are produced by neurons and glial cells. Unfortunately, currently, these types of strategies are expensive and require biosafety and must be regulated by turn on/off nanosystems expression.

Conclusion
The multifactorial nature of PD reflects the complex interaction of various cellular processes. The advance in the knowledge of the origin and impact of each related process (stress, neuroinflammation, and cell death) will allow us to better understand the degenerative process and consequently, progress in finding new therapeutic approaches.

Acknowledgment
This work was partially supported by Consejo Nacional de Ciencia y Tecnología (Catedra CONACYT # 1840) for DH-B, and the Instituto de Neuroetología from Universidad Veracruzana (DGI-174332015137) to MJR-H, and the Instituto Mexicano del Seguro Social (FIS/IMSS/PROT/G15/1480) to LMZ-F and PRODEP 29 (UANL-PTC-908) to AV-O. CJR-J received a fellowship from CONACYT for post-graduate studies in Neuroethology (#714879).

Conflicts of Interest
The authors declare that no competing interests exist.

References
1. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson’s disease: risk factors and prevention. Lancet Neurol 2016; 15:1257-1272.
2. Mostafa AA, Chakravarthy S, Phillips JR, Gupta A, Keri S, Polner B, et al. Motor symptoms in Parkinson’s disease: A unified framework. Neurosci Biobehav Rev 2016; 68:727-740.
3. DeMaagd G, Philip A. Parkinson’s Disease and Its Management: Part 5: Treatment of Nonmotor Complications. P T 2015; 40:838-846.
4. Sulzer D, Surmeier DJ. Neuronal vulnerability, pathogenesis,
and Parkinson’s disease. Mov Disord 2013; 28:715-724.
5. Hernandez-Baltazar D, Zavala-Flores LM, Villanueva-Olivo A. The 6-hydroxydopamine model and parkinsonian pathophysiology: Novel findings in an older model. Neurologia 2017; 32:533-539.
6. Villar-Cheda B, Valenzuela R, Rodriguez-Perez AI, Guerra MJ, Labandeira-Garcia JL. Aging-related changes in the nigral angiotensin system enhances proinflammatory and pro-oxidative markers and 6-OHDA-induced dopaminergic degeneration. Neurobiol Aging 2012; 33:204 e201-211.
7. Vogt Weisenhorn DM, Giesert F, Wurst W. Diversity matters - heterogeneity of dopaminergic neurons in the ventral mesencephalon and its relation to Parkinson’s disease. J Neurochem 2016; 139 Suppl 1-8.
8. Mazzone P, Lozano A, Stanzione P, Galati S, Scarmati E, Peppe A, et al. Implantation of human pedunculopontine nucleus: a safely and clinically relevant target in Parkinson’s disease. Neuroreport 2005; 16:1877-1881.
9. Okun MS. Deep-brain stimulation for Parkinson’s disease. N Engl J Med 2012; 367:1529-1538.
10. Hernández-Baltazar D, Zavala-Flores LM, Villanueva-Olivo A. The 6-hydroxydopamine model and parkinsonian pathophysiology: Novel findings in an older model. Neurologia 2017; 32:533-539.
11. Aquilonius SM, Nyholm D. Development of new levodopa constant-current device in Parkinson’s disease: an open-label, randomised controlled trial. Lancet Neurology 2012; 11:140-149.
12. Aiquilonius SM, Nyholm D. Development of new levodopa constant-current device in Parkinson’s disease: an open-label, randomised controlled trial. Lancet Neurology 2012; 11:140-149.
13. DeSousa RM, Schapira A. Safinamide: A new treatment for Parkinson’s disease. Expert Opin Pharma. 2017; 18:937-943.
14. Teo KC, Ho SL. Monoamine oxidase B (MAO-B) inhibitors: implications for disease-modification in Parkinson’s disease. Transl Neurodegener 2013; 2:19.
15. Borowicz JA. Side effects of a dopamine agonist therapy for Parkinson’s disease: a mini-review of clinical pharmacology. Yale J Biomed 2016; 89:37-47.
16. Stroyak A, Schapira A. Safinamide: A new treatment for Parkinson’s disease. Expert Opin Pharma. 2017; 18:937-943.
44. Duda P, Wisniewski J, Wojwrotzic T, Wojcicka O, Jaskiewicz M, Drolits-Fajdaks D, et al. Targeting GSK3 signaling as a potential therapy of neurodegenerative diseases and aging. Expert Opin Ther Targets 2018;11-16.

45. Shin EJ, Hwang YG, Sharma N, Tran HQ, Dang DK, Jang CG, et al. Role of protein kinase Cdelta in dopaminergic neurotoxic events. Food Chem Toxicol 2018; 121:254-261.

46. Kettenmann H, Kirchhoff F, Verkhratsky A. Microglia: new roles for the synaptic stripper. Neuron 2013; 77:10-18.

47. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal 2014; 20:1126-1167.

48. Tang Y, Le W. Differential Roles of M1 and M2 Microglia in neurodegenerative diseases. Mol Neurobiol 2016; 53:1181-1194.

49. Stefanis L. alpha-Synuclein in Parkinson's disease. Cold Spring Harb Perspect Med 2012; 2:a009399.

50. Altenhofer S, Kleikers PW, Radermacher KA, Scheurer P, Rob Hermans JJ, Schiffer S, et al. The NOX toolbox: validating the role of NADPH oxidas in physiology and disease. Cell Mol Life Sci 2012; 69:2327-2343.

51. Ma MW, Wang J, Dhandapani KM, Brann DW. NADPH Oxidase 2 Regulates NLRP3 Inflammasome Activation in the Brain after Traumatic Brain Injury. Oxid Med Cell Longev 2017; 2017:6057609.

52. Flores-Martinez YM, Fernandez-Parrilla MA, Ayala-Davila J, Reyes-Corona D, Blanco-Alvarez VM, Soto-Rojas LO, et al. Acute neuroinflammatory response in the Substantia Nigra pars compacta of rats after a local injection of lipopolysaccharide. J Immunol Res 2018; 2018:1839821.

53. Buffo A, Rite I, Tripathi P, Lepier A, Colak D, Horn AP, et al. Origin and progeny of reactive glios: A source of multipotent cells in the injured brain. Proc Natl Acad Sci U S A 2008; 105:3501-3506.

54. Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell 1999; 97:703-716.

55. Seri B, Garcia-Verdugo JM, Collado-Morente L, McEwen BS, Alvarez-Buylla A. Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. J Comp Neurol 2004; 478:359-378.

56. Kitamura Y, Inden M, Minamino H, Abe M, Takata K, Taniguchi T. The 6-hydroxydopamine-induced nigrostriatal neurodegeneration produces microgiglia-like NG2 glial cells in the rat substantia nigra. Glia 2010; 58:1686-1700.

57. Nadella R, Voutilainen MH, Saarma M, Gonzalez-Barrios JA, Leon-Chavez BA, Jimenez JM, et al. Transient transfection of human CDNF gene reduces the 6-hydroxydopamine-induced neuroinflammation in the rat substantia nigra. J Neuroinflammation 2014; 11:209.

58. Wright JW, Harding JW. Importance of the brain Angiottensin system in Parkinson's disease. Parkinsonis Dis 2012; 2012:860923.

59. Labandeira-Garcia JL, Garrido-Gil P, Rodriguez-Pallares J, Valenzuela R, Borrajo A, Rodriguez-Perez AI. Brain renin-angiotensin system and dopaminergic cell vulnerability. Front Neuroanat 2014; 8:67.

60. Rodriguez-Pallares J, Jirov CR, Parga JA, Guerra MJ, Labandeira-Garcia JL. Angiotensin II increases differentiation of dopaminergic neurons from mesencephalic precursors via angiotensin type 2 receptors. Eur J Neurosci 2004; 20:1489-1498.

61. Rodriguez-Pallares J, Rey P, Parga JA, Munoz A, Guerra MJ, Labandeira-Garcia JL. Brain angiotensin enhances dopaminergic cell death via microglial activation and NADPH- derived ROS. Neurobiol Dis 2008; 31:58-73.

62. Chao J, Yang L, Buch S, Gao L. Angiotensin II increased neuronal stem cell proliferation: role of AT2R. PLoS One 2013; 8:e34888.

63. Li J, Culman J, Hortnagl H, Zhao Y, Gerova N, Timm M, et al. Angiotensin AT2 receptor protects against cerebral ischemia-induced neuronal injury. FASEB J 2005; 19:617-619.

64. Garrido-Gil P, Rodriguez-Pallares J, Domínguez-Mejíde A, Guerra MJ, Labandeira-Garcia JL. Brain angiotensin regulates iron homeostasis in dopaminergic neurons and microglial cells. Exp Neurol 2013; 250:384-396.

65. Labandeira-Garcia JL, Rodriguez-Pallares J, Rodriguez-Perez AI, Garrido-Gil P, Villar-Chedda B, Valenzuela R, et al. Brain angiotensin and dopaminergic degeneration: relevance to Parkinson's disease. Am J Neurodegener Dis 2012; 1:226-244.

66. Munoz A, Garrido-Gil P, Domínguez-Mejíde A, Labandeira-Garcia JL. Angiotensin type 1 receptor blockade reduces l-dopa-induced dyskinesia in the 6-OHDA model of Parkinson's disease. Involvement of vascular endothelial growth factor and interleukin-1beta. Exp Neurol 2014; 261:720-732.

67. Rocha NP, Scalzo PL, Barbosa IG, de Campos-Carlin SM, Tavares LD, de Souza MS, et al. Peripheral levels of angiotensins are associated with depressive symptoms in Parkinson's disease. J Neurol Sci 2016; 368:235-239.

68. Villar-Chedda B, Costa-Besada MA, Valenzuela R, Perez-Costas E, Melendez-Ferro M, Labandeira-Garcia JL. The intracerebral angiotensin system buffers deleterious effects of the extracellular paracrine system. Cell Death Dis 2017; 8:e3044.

69. Jones LL, Yamaguchi Y, Stallcup WB, Tusznyski MH. NG2 is a major chondroitin sulfate proteoglycan produced after spinal cord injury and expressed by microglia and oligodendrocyte progenitors. J Neurosci 2002; 22:2792-2803.

70. Stallcup WB. The NG2 proteoglycan: past insights and future prospects. J Neurocytol 2002; 31:423-435.

71. Belachew S, Chittajallu R, Aguirre AA, Yuan X, Kirby M, Anderson S, et al. Postnatal NG2 proteoglycan-expressing progenitor cells are intrinsically multipotent and generate functional neurons. J Cell Biol 2003; 161:169-186.

72. Chung SH, Guo F, Jiang P, Pleasure DE, Deng W. Olig2/ Pppl-positive progenitor cells give rise to Bergmann glia in the cerebellum. Cell Death Dis 2013; 4:e5456.

73. Tripathi RB, River's LE, Young KM, Damen F, Richardson WD. NG2 glia generate new oligodendrocytes but few astrocytes in a murine experimental autoimmune encephalomyelitis model of demyelinating disease. J Neurosci 2010; 30:16383-16390.

74. Chari DM, Blaemore WF. Efficient relocalisation of progenitor-depleted areas of the CNS by adult oligodendrocyte progenitor cells. Glia 2002; 37:307-313.

75. Magnus T, Carmen J, Deleon J, Xue H, Pardo AC, Lepore AC, et al. Efficient recolonisation of demyelinating disease. J Neurosci 2010; 30:16383-16390.

76. Magnus T, Carmen J, Deleon J, Xue H, Pardo AC, Lepore AC, et al. Efficient recolonisation of demyelinating disease. J Neurosci 2010; 30:16383-16390.

77. Nait-Oumesmar B, Decker L, Lachapelle F, Avellana-Adalid Y, Bachelin C, Baron-Van Evercooren A. Progenitor cells of the adult mouse subventricular zone proliferate, migrate and differentiate into oligodendrocytes after demyelination. Eur J Neurosci 2014; 39:4357-4366.

78. Tamura Y, Kataoka Y, Cui Y, Takamori Y, Watanabe Y, Yamada H. Multi-directional differentiation of doublecortin- and NG2-immunopositive progenitor cells in the adult rat neocortex in vivo. Eur J Neurosci 2007; 25:3499-3498.

79. Chavin D, Medori R, Hauser RA, Rascol O. Therapeutic strategies for Parkinson disease: beyond dopaminergic drugs. Iran J Basic Med Sci, Vol. 22, No. 7, Jul 2019
80. Carrascal L, Nunez-Abades P, Ayala A, Cano M. Role of melatonin in the inflammatory process and its therapeutic potential. Curr Pharm Des 2018; 24:1563-1588.

81. Sanchez-Barcelo EJ, Rueda N, Mediavilla MD, Martinez-Cue C, Reiter RJ. Clinical Uses of Melatonin in Neurological Diseases and Mental and Behavioural Disorders. Curr Med Chem 2017; 24:3851-3878.

82. Martinez B, Peplow PV. Neuroprotection by immunomodulatory agents in animal models of Parkinson's disease. Neural Regen Res 2018; 13:1493-1506.

83. Wang YL, Ju B, Zhang YZ, Yin HL, Liu YJ, Wang SS, et al. Protective effect of curcumin against oxidative stress-induced injury in rats with Parkinson's disease through the Wnt/beta-catenin signaling pathway. Cell Physiol Biochem 2017; 43:2226-2241.

84. Ullah H, Khan H. Anti-Parkinson potential of silymarin: mechanistic insight and therapeutic standing. Front Pharmacol 2018; 9:422.

85. Zanforlin E, Zagotto G, Ribaudo G. The medicinal chemistry of natural and semisynthetic compounds against Parkinson’s and Huntington’s diseases. ACS Chem Neurosci 2017; 8:2356-2368.

86. Kirik D, Cederfjall E, Halliday G, Petersen A. Gene therapy for Parkinson’s disease: Disease modification by GDNF family of ligands. Neurobiol Dis 2017; 97:179-188.

87. Pignataro D, Sucunza D, Rico AJ, Dopeso-Reyes IG, Roda E, Rodriguez-Perez AI, et al. Gene therapy approaches in the non-human primate model of Parkinson’s disease. J Neural Transm (Vienna) 2018; 125:575-589.