Review Article

International Journal of Neurology and Neurosurgery
Volume 9 Number 2, July - December 2017
DOI: http://dx.doi.org/10.21088/ijnns.0975.0223.9217.16

Parkinson's Disease and Therapeutic Strategies

Rajesh Singh Pukhrambam*, Abuno Thepa, Nukshimenla Jamir**, Limamanen Phom**, Sarat Chandra Yenisetti*****

Abstract

Parkinson's disease is the second most common aged associated neurodegenerative disorder after Alzhiemer affecting approximately 1% of the population above the age 50. James Parkinson for the first time medically described Parkinson disease as a neurological disorder in his famous work "An Essay of the shaking palsy". The pathological hallmark of PD is selective and progressive degeneration of dopaminergic neurons in the *substantia nigra pars compacta* of human brain and the accumulation of Lewy bodies in the surviving neurons. Cardinal symptoms of Parkinson's disease include resting tremor, rigidity, postural instability. Besides motor symptoms, several non-motor symptoms are manifested many years before the onset of motor symptoms. Parkinson's disease is classified into sporadic and familial PD. Therapeutic strategies prior to Levodopa and Deep Brain stimulation include bloodletting from the neck, vesicatories, shaking chair, hydrotherapy, spa treatments, light exercise and treating with hyoscyamine, arsenic, morphia, conium, Indian hemp" (cannabis). Though levodopa is the leading treatment for PD, it has many limitations. Stem cell therapy appears to be a promising therapy to replenish degenerated dopaminergic neurons.

Keywords: Parkinson's Disease; Motor Symptoms; Non-Motor Symptoms; Deep Brain Stimulation; Levodopa; Stem Cell Therapy; Biomarkers.

Introduction

Parkinson's disease (PD) is the second most common aged associated neurodegenerative disorder after Alzheimer disease, affecting approximately 1% of the population above the age of 50. It is believed that 7–10 million people worldwide are suffering from PD [1]. Studies have shown that prevalence of PD in men is higher (one and half times more) than that of women [2]. With the increased in the life expectancy of the world population, numbers of PD patients are also expected to double by 2030 [3], posing a major health care burden.

Author's Affiliation: *Assistant Professor and Research Scholar, **Research Scholar, ***Associate Professor, *Drosophila* Neurobiology Laboratory Department of Zoology, Nagaland University (Central) Lumami, Nagaland 798627, India.

Reprint Request: Sarat Chandra Yenisetti, Associate Professor, *Drosophila* Neurobiology Laboratory Department of Zoology, Nagaland University (Central) Lumami, Nagaland 798627, India.
E-mail: yschandrays@rediffmail.com
Sarat@nagalanduniversity@ac.in

Received on 14.03.2017, **Accepted on** 25.03.2017

© Red Flower Publication Pvt. Ltd.

The Indian traditional systems of medicine "Ayurved" texts from about 1000 BC provide descriptions which suggest the existence of symptoms similar to PD [4]. Ancient Chinese, inner canon yellow emperor, sources from about 450-500 BC also mention the treatment of diseases which are similar to PD [5]. Several other sources, including an Egyptian papyrus, the Bible and Galen's writings describe symptoms resembling those of PD [6]. Much later in 1817, James Parkinson, an English doctor, published his famous work "An Essay of the shaking palsy" reporting six cases of paralysis agitans. His essay for the first time described the symptoms of paralysis agitans [7,8]. Early neurologists who have contributed to the knowledge of the disease include Erb, Trousseau, Kinnier, Gower and Jean-Martin Charcot who, later, recognized the importance of James Parkinson's work and named the disease after him [8].

The pathological hallmark of PD is selective and progressive degeneration of dopaminergic neurons (DAn) and the accumulation of Lewy bodies (LB)(intracellular cytoplasmic proteinaceous inclusions) in the *substantia nigra* (SN) of the mid brain resulting in dopamine deficiency in the brain. Alpha synuclein (α-syn) is the major component of LB and

may act as a toxic factor mediating the pathology of PD [9]. Clinical signs of PD include resting tremor, bradykinesia, rigidity and postural instability. It can cause the patients to develop a forward or backward lean due to the loss of postural reflexes [10]. Besides these major motor symptoms, PD is usually associated with numerous non-motor symptoms (NMS).

Despite intensive and extensive studies conducted worldwide, the etiology of PD remains unclear. Although genetic elements and exposure to environmental toxins, such as herbicides, pesticides, and heavy metals are thought to play a crucial role in disease onset, ageing remains the predominant risk factor [11]. 95% PD patients is believed to have a sporadic component. Some studies suggest that environmental factors may be more important than that of the genetic factors in familial aggregation of PD. In most of the PD cases, the cause is environmental influence, probably toxins,and sustained neuronal loss due to progressing age [12]. Observing PD in 1-methyl-4- phenyl- 1,2,3,6- tetrahydropyridine (MPTP) drug users regenerated curiosity in reassessing environmental influences [10].

Current therapeutic strategies for PD mitigate symptoms by the replacement of dopamine, with variable efficacy and considerable side effects. Levodopa (L-dopa) is a dopamine precursor and is the leading treatment of PD for over 40 years. L-dopa improves motor impairment by enhancing dopamine levels [13]. However, prolong use of L-dopa leads to other motor dyskinesia (a category of movement disorders that are characterized by involuntary muscle movement) that undermine the benefits of treatment. Surgery has been used to reduce motor symptoms in advance cases where drugs are ineffective [14]. The development of effective treatment for PD is difficult because pathology is believed to be affected by several pathways. However, there are currently no established curative or preventive interventions, stemming from a poor understanding of the molecular mechanism(s) of the pathogenesis.

Pathological features

Non-Motor Symptoms(NMS)

NMS are the symptoms, which do not involve motor coordination of the central nervous system (CNS). NMS are manifested many years before the onset of motor symptoms in the patients of PD. NMS are commonly prevalent in a large proportion of PD patients, but these NMS are often overlooked in clinical practices due to lack of complaints by the patients. These symptoms include neuropsychiatrics symptoms (mental disorder and behavioral changes), sleep disorders (a medical disorder of the sleep patterns of a person or animal), fatigue (a subjective feeling of tiredness which is distinct from weakness and has a gradual onset), sensory symptoms (may affect sense like hearing, touch and taste), autonomic dysfunction (affect a small part of the autonomic nervous system or the entire autonomic nervous system), gastrointestinal symptoms (symptoms related to gastrointestine), dopaminergic drug induced behaviour (non-motor fluctuation dysautonomia) and other symptoms [15].

Some of the NMS such as olfactory, fatigue, REM sleep behavior disorders, constipation, pain and depression appear at the early stage of the disorder and occur throughout the course of the disease. The frequency of NMS increases with the progress of the disease. Some non-dopaminergic neurotransmitters such as serotonergic, noradrenergic and cholinergic transmission are involved in most of the non-motor symptoms conjugated with PD [16].

Major NMS and related sub symptoms associated with PD pathology are listed in Table1.

Motor symptoms

Motor symptoms (MS) typically involve a loss of motor coordination or lead to restricted mobility. MS include resting tremor, rigidity, bradykinesis and postural instability.

Resting Tremor: In the initial stages of the disease, about 70% of patients experience a mild tremor in the hand or foot or less commonly in the jaw or face. A typical onset is shaking in one finger. The tremor comprises shaking or oscillating movement, and usually appears when a person's muscles are at rest, hence the name "resting tremor." The affected body part trembles when it is not performing any function. Typically, the fingers or hand will tremble when folded or when the arm is held loosely at the side.

Bradykinesia: Bradykinesia "slow movement" describes as a general reduction of spontaneous movement, which gives the appearance of abnormal stillness and reduce in facial expressivity. Bradykinesia causes difficulty with repetitive motion, such as finger tapping. Due to bradykinesia, patients with Parkinson's may have difficulty in performing everyday functions, such as buttoning a shirt, cutting food or brushing teeth. Patients who experience bradykinesia may walk with short, shuffling steps. Bradykinesia can affect a person's speech too, which may become quieter and less distinct as Parkinson's progresses.

Table 1: Major Non-motor symptoms and related sub symptoms associated with Parkinson's disease (PD) (modified from Bonnet et al 2012)

SL. No	Major NMSs	Related sub Symptoms
01.	Neuropsychiatric symptoms	Depression, anxiety, apathy, hallucination, attention deficit, cognitive impairment, dementia, dopaminergic dysregulation syndrome (usually related to L-dopa), impulse control disorders, panic attacks.
02.	Sleep Disorders	Random eye movement (REM), sleep behaviour disorder (possible premotor symptoms) , excessive daytime somnolence, narcolepsy type "sleep attack", restless legs syndrome, periodic leg movements, insomnia, sleep disordered breathing, non-REM parasomnias (confusional wandering)
03.	Fatigue	Central fatigue (may be related to dysautonomia), peripheral fatigue.
04.	Sensory symptoms	Pain, olfactory disturbance, hyposmia, functional anosmia, visual disturbance (blurred vision, diplopia; impaired contrast-sensitivity).
05.	Autonomic dysfunction	Bladder dysfunction (urgency, frequency, nocturia), sexual dysfunction, sweating abnormalities (hyperhydrosis), orthostatic hypotension.
06.	Gastrointestinal symptoms	Dribbling of saliva, dysphagia (choking), agueusia, constipation, nausea, vomiting.
07.	Dopaminergic drug induced behavior	Hallucinations, psychosis, delusions, dopamine dysregulation syndrome, impulse control disorders.
08.	Non-motor fluctuation	Dysautonomia, cognitive/psychiatric, sensory/pain, visual blurring
09.	other symptoms	Weight loss

Rigidity: Rigidity is the stiffness and inflexibility of the limbs, neck and trunk. Muscles normally stretch when they move, and then relax when they are at rest. However, in Parkinson's rigidity, the muscle tone of an affected limb remains stiff and does not relax, sometimes contributing to a decreased range of motion. PD patients commonly experience tightness of the neck, shoulder and leg. A person with rigidity and bradykinesia does not swing his or her arms when walking. Rigidity can be uncomfortable or even painful.

Postural Instability: Patients with postural instability have lost some of the reflexes required for maintaining an upright posture, and may lean backward if jostled even slightly. Some develop a difficult tendency to sway backward when rising from a chair, standing or turning. This problem may result in a backward fall. People with balance problems may have particular difficulty when making turns or quick movements. Doctors test postural stability by using the "pulltest."

Types of PD

On the basis of causes, PD can be classified into"Sporadic PD and Familial PD". Researchers think that mitochondrial dysfunction, oxidative stress, protein misfolding play a central role in PD pathogenesis but, the exact pathogenic mechanisms leading to selective DAn death in PD remain poorly understood and it appears to involve both genetic (familial) and environmental factors (sporadic).

Sporadic Parkinson's Disease

Sporadic PD is a disease that is occurring randomly in a population with unknown cause. In sporadic PD, the cause is considered to be environmental although the familial factor is also present, suggesting that the pathogenesis of PD is likely to be multifactorial which may involve gene–environment interactions. The discovery of MPTP, induces pathological features of idiopathic PD by affecting the nigrostriatal system [17], pesticide (rotenone) and herbicide (paraquat), has implicated environmental toxins in the induction of sporadic PD [18,19]. Both epidemiological and experimental studies suggest that the potential involvement of specific agents such as neurotoxicants (pesticides) or neuroprotective compounds (coffee and tobacco products) in the pathogenesis of nigrostriatal degeneration, further supporting a relationship between the environment and PD [20].

The studies of environmental risk factors of PD are not an easy task because interactions of environmental toxins and gene–environment may occur well before the onset of clinical symptoms since it remains undetected for many years. Moreover, neurodegenerative changes that underlie the symptoms of PD may be the result of combined effects of multiple exposures and these effects could have been compounded by increased vulnerability of the ageing nigrostriatal system to toxic injury over the years. Epidemiological and case–control studies suggest that rural living, well water drinking, use of pesticides, and certain occupations (farming, mining, and welding) are associated with an increased risk of PD [21–23]. Epidemiological studies reveal that

Table 2: Demonstrated neuroprotective efficacy of certain natural products and implicated biochemical and molecular pathways

Agents	Mechanism	Molecular pathways
Resveratrol	Anti-inflammation	Decrease the mRNA levels of IL-1α and TNFα [96]; decrease the levels of COX-2 expression [97]; decrease the levels of NO, TNF-α, IL-1β, IL-6, MCP-1; suppress production of IL-12p40, IL-23 and C- reactive protein, and respective receptors [98]; down-regulate MPO; modulate the activity of PGC-1α, Akt and NF-κB [99,100].
	Anti-apoptosis	Reduce the activity of caspase-3 and the level of Bax [101]; regulate DNA fragmentation and the mRNA levels and protein expression of Bax, Bcl-2, cleaved caspase-3, and cleaved ARP-1 [102]; activate sirtuin deacetylases and PPAR-γ [103,104]
	Anti-oxidation	Diminish superoxide anion [105]; inhibit ROS (Reactive oxygen species) generation [106]; up- regulate the antioxidant status and the expression of MsrA [103]; activate PPAR-γ, AMPK, SIRT1; raise the mRNA expression of PGC- 1α's target genes [107]
	Neurotrophic effect	Increase neurotrophic factors release in the concentration- and time- dependent manners [108]
Curcumin	Anti-inflammation	Inhibit NF-κB translocation [105]and AP-1 activation [109]; inhibit the protein expression of GFAP [110] and iNOS, decrease activation of astrocytes and microglia [111], reduce pro-inflammatory cytokine, alleviate loss of TH-IR fibers, protect axon [112]
	Anti-apoptosis	Reduce MMP loss, attenuate MPP(+)-induced an increase in intracellular ROS level, induce over expression of BCl-2 and antagonize MPP+-induced over expression of iNOS; [113] ease alpha S induced toxicity [114]; protect DAn axon [115]; decrease the Bax/Bcl-2 ratio[116]; reduce the accumulation of A53T α-syn[117]; inhibit the JUN/c-Jun pathway[118]; block MPP(+) [119]
	Anti-oxidation	Restore membrane potential, increase level of Cu-Zn superoxide dismutase, suppress ROS [105]; sustain SOD1 level [111]; reduce the levels of p-p38, cleaved caspase-3 and quinoprotein formation [121]; restore depletion of GSH levels [122], free radical scavenging [123]; inhibit oxidative stress and the mitochondrial cell death pathway [124]; activate the Nrf2/ARE pathway [125]; reduce p53 phosphorylation [126]
	Prevent α-synuclein aggregation and fibrillation	Prevent α-synuclein aggregation and fibrillation [127]; destabilize preformed alpha S [128]; specifically binds to oligomeric intermediates [129];
	Inhibit MAO-B	Inhibit MAO-B activity[127]
	Anti-Inflammation	Suppress NO production and TNF-α secretion, inhibit the mRNA expressions of iNOS, TNF-α,IL-1β, COX-2 and MMP-9, inhibited the phophorylations of PI3K/Akt and MAPKs and the DNA binding activities of NF-kB and AP-1 [130],; suppress phosphorylation and nuclear translocation of NF-κB/p65, phosphorylation and degradation of IκB and the phosphorylation of IKK;inhibit the activation of Akt and ERK1/2 [131]; reduce NO-formation and PGE2 synthesis [132]; attenuate upregulation TNF-α, IL-1β and IL-6 mRNA, and iNOS and COX-2 expression [133]
	Anti-Apoptosis	Inhibit the activation of caspase-3, reduce iNOS and NO production [134] ; increased the phosphorylation,inhibition of Bad through activation of the PI3K/Akt pathway [135]; Enhance theexpression of Bcl-2 protein and mRNA, reduce the expression of Bax, Bax mRNA, and iNOS, and attenuate the cleavage of caspase-3 [136]
	Anti-oxidation	Reduce the generation of ROS and cytochrome c release[134], restore mitochondrial membrane potential, increased the phosphorylation inhibition of Bad through activation of the PI3K/Akt pathway [136] decrease iron influx, inhibit IRPs; decrease DMT1-mediated ferrous iron uptake and iron-induced cell damage [137,138]
	Neurotrophin-like effects	Increase neurite outgrowth; reversed MPTP-induced cell death [139]
	Neuroprotective activity	When administered orally to mentally retarded children showed significant increase in general ability and behavior patterns [140]. It improves brain power [142,143] and decreased the levels of norepinephrine, dopamine, 5-HT, and their metabolites in the brain [141,144]
	Neuroprotective activity	Is used in traditional method for epilepsy, constipation, cough, fever, clearing voice, diabetes, and mental disorders [145]; the neuroprotective effect on lipofuscinogenesis and fluorescence product in the brain of D-galactose-induced ageing accelerated mice [146,141]
	Neuroprotective activity	Treating a number of ailments like epilepsy, mental ailments, abdominal tumors, kidney and liver troubles, etc. [147]; the hydroalcoholic extract of rhizomes against middle cerebral artery occlusion (MCAO)-induced ischemia; found to have significant improvement in neurobehavioral performance associated with significant reduction in malondialdehyde levels in the cortex and increase in glutathione as well as superoxide dismutase activity in the cortex and corpus striatum in rats [146,141]

Table 3: Classification of biomarkers

	Biomarker Type	Related Symptoms
1	Behavioural biomarkers	Depression [160], sexual dysfunction, altered circadian rhythm (sleep wakeful cycle), micrographia (small words), incontinence, deafness, agraphia (impaired handwriting), acalculia (difficulty solving simple calculation due to dementia) [159]
2	Sensory biomarkers	Olfactory deficit discrimination, hypoguesia deafness (loss of hearing), impaired visio-spatial and color discrimination, hypoguesia (loss of taste) [159].
3	Cognitive biomarkers	Agraphia, acalculia [159]
4	Motor biomarkers	Resting tremor, postural instability, muscular rigidity, bradykinesia [159]
5	Omics biomarkers	α-syn, DJ-1, miRNA [159]

exposure to rotenone and MPTP leads to PD at later stages of life. Further experimental data substantiates that rotenone is a complex I inhibitor. Therefore rotenone exposure disrupts ATP synthesis leading to the death of DAn in PD patients [24,25].

Mechanisms of Environmental toxins

Discovering of MPTP causing Parkinsonian syndrome triggered to investigate further for environmental factors as potential causes of PD. Epidemiological studies have suggested that environmental toxins are one of the major causes of sporadic PD [26]. The mechanisms by which the neurotoxins induce PD like symptoms are briefly described below.

MPTP: It is a metabolite of the drug heroin and is transported across the blood–brain barrier (BBB) by dopamine transporter (DAT) of plasma membrane and once it crosses the BBB, MPTP is metabolically activated to the fully oxidized 1 methyl 4-phenylpyridinium species (MPP+) which is then taken up into DAn via DAT [27,28]. After MPP+ entering into DAn, it is accumulated into synaptic vesicles via the vesicular monoamine transporter (VMAT2) [29]. The ratio of DAT to VMAT2 indicates the sensitivity of DAn to toxic injury[30].

6 Hydroxy dopamine (6 OHDA): 6 OHDA, catecholaminergic neurotoxin, causes severe loss of dopamine neurons within a day in mouse model of PD [31]. Inside neurons, 6 OHDA produces ROS and quinones that inactivate biological macromolecules. Till date, no LB like inclusion has been observed in the 6-OHDA model.

Paraquat (PQ): One of the most commonly used herbicides in the world is PQ. The structural similarity of PQ with MPP+ suggested that PQ might be dopaminergic neurotoxicant which may lead to PD. PQ is suspected to carry to the brain by neutral amino acid transporters and subsequently the cells in a sodium dependent fashion [32]. Once within cells of the CNS, PQ acts as a redox cycling compound at the cytosolic level, which potentially leads to indirect mitochondrial toxicity [33]. Recent studies have shown that PQ induced apoptosis involves Bak protein, a pro apoptosis Bcl 2 family member [34-38].

*Rotenone (ROT):*ROT is a crystalline isoflavone used as an insecticide. Inhibition of complex I of mitochondrial electron transport chain (METC) by ROT has been widely used to study the role of the METC in apoptosis [39,40]. The METC is the major site of ATP synthesis in eukaryotes and it also plays an important role in apoptosis [41-43]. It is now known that upon apoptotic stimulation, mitochondria release several proapoptotic regulators, such as cytochrome c [44], Smac/Diablo [45,46], endonuclease G [47], and apoptosis inducing factor [48] to the cytosol. These proapoptotic regulators will then activate cellular apoptotic programs downstream [41-43]. The release of proapoptotic regulators is further regulated by the translocation of Bcl 2 family proteins [49,50].

Maneb (MB): MB, a commonly used fungicide, causes an irritant to respiratory tracts and is capable of inducing sensitization by skin contact. Mechanistically, MB can cross the BBB. Although knowledge of the mechanisms of this toxin is very limited, MB inhibits mitochondrial complex III [51]. Further, MB was shown to induce apoptosis through Bak activation, whereas combination of PQ and MB inhibits the Bak dependent pathway while potentiating apoptosis through Bak protein [52].

*Heavy metals (HM):*HM are metals with relatively high densities, atomic weight or atomic numbers. HM such as iron, manganese, copper, lead, aluminium, zinc, etc. can affect the DAn in the SN and increase oxidative stress. Exposures to these heavy metals increase the risk of PD. Chronic exposure to high levels of manganese in manganese miner's cause accumulation of this metal in the basal ganglia, leading to tremors, rigidity and psychosis that mimic PD [53,54]. The potential role of iron and other transition elements has also been studied. The level

of ferritin in PD patients was found to be decreased. Hence iron accumulation together with decrease binding capacity may increase the risk for iron mediated toxic reactions in PD by generating the highly toxic hydroxyl radical in the presence of iron and hydrogen peroxide, leading to oxidative stress and neurodegeneration.

Genetics/Familial PD

Familial PD is caused by the mutation of genes. Familial PD cases are much less observed compared to sporadic PD cases. Mutations occur in a number of genes such as α-syn [55], Parkin (PARK2)[56], PTEN-induced putative kinase 1 (PINK1) [57] , leucine- rich repeat kinase 2(LRRK2) [58], DJ-1[59] and ATP13A2[60]. Among the genetic cases, autosomal dominant genes are α-syn and LRRK2 and the rest are known as autosomal recessive genes. Studies of familial forms of PD suggest that α-syn plays a crucial role in the development of the disease. Excess α-syn gene produce extra α-syn protein which damage neurons. The harm is more pronounced in DAn of SN which plays a key role in controlling normal movement in PD. Further, the identification of the mutated α-syn gene causing familial PD [61] as a risk factor for sporadic disease provides a genetic context for the disease. The finding of α-syn as a key component of the Lewy body[62] further links this gene to potential molecular mechanisms of PD.Studies on Parkin and PINK1 of Drosophila mutants have suggested that mitochondrial dysfunction is the major cause for the PD pathogenesis and that these two PD genes are in a common pathway with Parkin downstream of PINK1. All the known genetic mutations linked to PD are directly or indirectly implicated in mitochondrial homeostasis, energy metabolism, response to oxidative stress or proteomes functional pathways or endoplasmic reticulum stress response.

Therapeutic strategies

Early nineteenth century, James Parkinson suggested venesection, specifically bloodletting from the neck, followed by vesicatories to induce blistering and inflammation of the skin [63]. Efforts were framed to decompress the medulla in order to divert blood and inflammatory pressure away from the brain and spinal cord. In the mid-1800s, Jean-Martin Charcot was also the first to suggest the use of the term "Parkinson Disease"[64] and suggested vibratory therapy for treatment of PD where he developed a replication device which provide rhythmic movement by an electrically powered "shaking chair" [65]. Other therapies includes hydrotherapy, spa treatments, light exercise, electrical incitement by faradic, galvanic, or direct spark (franklinization) were used to stimulate weakened muscles. In PD patients, rigidity and some sensory symptoms improved, but not in tremor. For tremor, Gower used hyoscyamine, arsenic, morphia, conium (hemlock), and "Indian hemp" (cannabis) as agents for temporary decline in tremor [66]. Precisely noting on the power of cannabis and opium Gower stated: "I have several times seen a very distinct improvement for a considerable time under their use."[67]. Presently, cannabis have some dopaminergic activation properties, but use of opium affects the motor system in a generalized manner without direct or primary dopaminergic involvement [68].

Levodopa

L-3,4-dihydroxy- phenyl-L-alanine(L-dopa), a precursor of dopamine, is used in place of dopamine as dopamine cannot pass the BBB.It is administered either orally or intravenously where it gets converted to dopamine before it reaches to brain, hence it is administered with another substance called carbidopa (decarboxylase inhibitor). Addition of carbidopa decreases the amount of L-dopa that is required and may reduce some of its side effects such as nausea and vomiting by reducing the supply of free dopamine outside the brain. Carbidopa reduces the amount of needed L-dopa and delays the conversion of L-dopa into dopamine until it reaches the brain, preventing some of the side effects that often accompany L-dopa therapy. L-dopa is a very useful drug for reducing the tremors and other symptoms of PD during the early stages of the disease. Its use is associated with improved mobility, reduced disability and life expectancy of L-dopa treated patients is markedly increased. A high-protein diet can interfere with the absorption of L-dopa, so physicians restrict patients in taking protein-rich meals during their early stages of the treatment [69].

With the knowledge that L-dopa was the natural precursor to dopamine, Birkmayer received Hornykiewicz's supply of laboratory L-dopa and injected it intravenously for the first time to Parkinsonian patients in 1961. He observed that, bed-ridden patients who were unable to sit up, patients who could not stand up when seated, and patients who when standing could not start walking performed all these activities with ease after L-dopa. They walked around normally and could even run and jump [70]. L-dopa is a naturally occurring amino acid, where researchers have found L-dopa containing compounds in early medicine. Mushroom tyrosinase has been commercially used in the enzymatic synthesis of L-dopa by enzyme immobilization [71]. It lowers the production cost due

to the reusability of the enzymes. Cowage or cowitch plant (*Mucunapruriens*) is known under the name of Atmagupta in Sanskrit and contains L-dopa [72]. These developments have been based on the logical understanding of the dopamine system, metabolic pathways, and receptor populations.

Limitations

Long-term treatment leads to abnormal involuntary movements known as L-dopa-induced dyskinesia , which are uncontrolled and repetitive movement in the axis, arms, legs and oro- facial zone [73,74]. These complications occur in about 50% of L-dopa-treated patients who have received the drug for more than 5 years, in 80% of patients treated for 10 years, and in nearly all patients with young onset disease [75,76,77] Patients have to suffer a variety of side effects; most commonly are nausea, vomiting, low blood pressure and restlessness. The repeated pulsatile stimulation of striatal dopamine receptors with chronic oral L-dopa treatment induces plastic changes in basal ganglia circuits that can lead to the development of motor response complications. A serious concern regarding L-dopa is that it causes hallucinations and psychosis after long-term use. Some patients exhibit severe dyskinesia soon after taking low doses of L-dopa and chronic treatment does more harm since L-dopa itself is a pro-oxidant which could contribute to tissue damage due to oxidative stress in PD and other neurological disorders. There are controversies in the treatment, whether it causes the motor complications or it is toxic to DAn, but it has not yet been proven and clinical trials have not clarified this situation.

Deep Brain stimulation (DBS)

DBS was first experimented in animal about 70 years ago and has been used in human subjects, mainly to treat movement disorders. It is a kind of pacemaker, a battery-operated medical device called a neurostimulator (usually implanted under the skin near the collarbone, in some cases it may be implanted lower in the chest or under the skin over the abdomen) that involves implanting of the electrodes within specific brain circuits to modulate the activity of those circuits, either to suppress pathological neuronal activity or to drive inactive output [78]. Stimulation through an electrode placed within a nuclear region will affect several neuronal cell components [79]. The target location is often choosed using structural neuroimaging, usually computed tomography or magnetic resonance imaging. This approach has been used to guide electrode placement for patients with depression, cluster headache, and epilepsy [80]. There are many brain targets, mainly the subthalamic nucleus (STN) and also the globus pallidus interna that the DBS electrode may be placed within, which have been approved by Food and Drug Administration in 2002 for use in PD. DBS changes the rate of signal and pattern of individual neurons in the basal ganglia [81] and eliminates abnormal rhythmic oscillation between the cortex and the basal ganglia [82]. The electrical current also acts on synapses and triggers adjacent astrocytes releasing calcium and to promote neurotransmitters (adenosine and glutamate) from excitatory efferent neurons [83]

- Additionally, this has an overall increase in cerebral blood flow [84] and stimulates neurogenesis [85]. DBS depend on a number of parameters, including stimulation, physiological properties of the targeted cells, structural configuration of the electrode and the surrounding tissue, and possibly the fundamental pathophysiology of different disease states [86]. However, still it remains uncertain of how these influences lead to changes in the symptoms of a certain neurological disease. Therefore, the foundation of this therapy has been more or less observational.

Limitations

The most adverse events associated with placement of leads for DBS are infection and intracranial hemorrhage. It also includes acute or chronic neurological and neuropsychological complications such as surgery, hardware and stimulation and was found that the overall incidence of hemorrhage was 5.0%, with symptomatic hemorrhage occurring in 2.1% of patients and hemorrhage resulting in lack of permanent neurological activities or death in 1.1% [87]. Postoperative seizures have also been reported and usually occur within 48 hrs of surgery [88], with an estimated incidence of 2.4% [89]. The most common hardware complications include infections, migrations or misplacements of the electrodes, wire fractures, skin erosion and device malfunction [90], which often require device removal and a period of antibiotic treatment before consideration for device replacement [91]. Stimulation-related side effects include muscle contractions, dysarthria, ocular deviations, tremor, dyskinesia, headache, pain and paresthesia [92]. Verbal fluency is the most common cognitive adverse effect of STN DBS, caused by surgical electrode implantation rather than stimulation-induced interference [93]. Changes in medication, neuronal plasticity following DBS,

adaptation difficulties induced by the motor effects of DBS shows chronic effects mania, depression, apathy, panic, impulsivity, anxiety, hallucinations, and even suicidal thought [94]. In general, DBS is a relatively safe approach associated with low rate of side effects, which is an effective therapeutic option to assist in a multitude of otherwise treatment-resistant neurological diseases.

Natural Remedies to Parkinson's Disease

Studies have now shown that polyphenols play a pivotal role in mediating the therapeutic actions of these herbal products. Polyphenols are natural compounds with antioxidant properties, present in plants, vegetables and fruits. They represent secondary plant metabolites synthesized to defend against microbial attack, pests and harmful radiations, in addition to providing the plant with brilliant colors and fragrance. Natural polyphenols vary from simple molecules (phenolic acids) to complex polymeric forms (condensed tannins) [95]. Some of the major plant derived products suggested as therapeutic agents for PD are shown in Table 2.

Stem Cell Therapy (SCT)

SCT is the use of stem cells (SCs), undifferentiated cells of a multi-cellular organism, to treat or to prevent a disease. SCs have multilineage differentiation potential and maintain self- renewal and proliferative ability that enables the researcher to replace the degenerated neuron and enhancing the levels of dopamine through regeneration of DAn, which leads to the creation of conditions to model inherent features in the pathogenesis of PD.

At present, there are two types of grafts resources for PD: allogenic and autogenous. Allografts include fetal brain or other human embryonic tissues and human embryonic stem cell (hESC) derived DAn while autologous grafts derived from patient-specific somatic cells via in vitro induced pluripotent stem cells(iPSC) reprogramming or direct lineage conversion. DAn from fetal ventral mesencephalic tissues were the major cell replacements in the implemented clinical trials.

The development of new cell models of PD is a particularly promising area of SCT. New advances in stem-cell technology have been acquired from pure PD patient's homogeneous generation of induced DAn such as hESc-derived Dan [149,150] iPSc-derived Dan [148,149,150] and directly reprogrammed DAn [151]. This technology provides an opportunity for the cellular events under genetically defined condition to be investigated in a human context. Compared with animal models, stem-cell models have achieved the following breakthroughs in mimicking the microenvironment of the PD cell in vitro. First, studies suggest that patient-specific derived cells still retain an epigenetic memory [152] (the topological memory) [153] and keep expressing the carrying transcriptomic disease-causing mutation memory [154,155]. Second, the isogenic cells from healthy patients were procured from patient-specific cells via a genome-editing technique, providing a method for single-factor analysis to study observed PD phenotypes caused by a certain PD-causing mutation. Third, on the basis of generation of pure lines of iDAn with genetic variants, scientists could mimic mono-factorial environmental stress–related neurodegenerative states by imposing artificial stress factors on pathological processes of PD [156,157].

Limitations

Despite many advantages of SCT, many questions and obstacles exist in the therapeutics of stem cells. The Major challenges of the clinical use of stem cells include ethical questions, tumorigenesis, immune response, and toxicity to a degree. There are many ethical issues and intense immune response in the use of ESCs. Compared with ESCs, iPSCs have lesser ethical issues and reduced immune rejection, but because of powerful pluripotency, the risk of tumor development of iPSCs is greater than that of other stem cells. Morever, iPSCs derived from autologous PD patients may carry pathogenic gene mutations that affect the prognosis for cell-replacement therapy. To obtain a higher rate of survival and integration, the details of canonical grafting procedures need to be estimated. In spite of significant limitations of stem cell therapeutics, it throws a great promise to replenish the degenerated DAn in PD patients.

Biomarkers

National Institutes of Health (NIH) working group (2011) defined biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". Biomarkers are tools that are used to indicate or evaluate the progress of a disease or the effects of treatment. Biomarkers facilitate early diagnosis, disease prevention, drug target identification, and drug response[158]. PD biomarkers include (1) preclinical biomarkers; and (2) clinical biomarkers [159](Classification of biomarkers is given in Table 3). The most biomarkers could be used for diagnosis, tracking disease

progression, and development of effective treatments of PD through clinical symptoms and neuroimaging, a number of genetic and biological markers from blood and CSF may hold promise for the early diagnosis of PD.

New approaches such as transcriptomics, proteomics, metabolomics have been an integral part in identifying pathways that are related with dopaminergic neurodegeneration and subsequently PD. Molecular biomarkers include nucleic acid-based biomarkers such as gene mutations or polymorphisms, gene expression analysis, peptides, proteins, lipid metabolites, and other small molecules. Transcriptomics have reliably identified alterations in pathways in the *SN pars compacta* and blood of PD subjects associated with mitochondrial and proteasomal function, dopamine neurotransmission and oxidative stress. In addition, it has uncovered the axon guidance pathway as a potential contributor to dopaminergic neurodegeneration. The use of proteomics has provided a comprehensive characterization of the human midbrain, as well as the protein composition of human cerebrospinal fluid. This platform has been further utilized to identify specific proteins and pathways that are altered in the biofluids of PD compared with controls. Metabolomics-based studies of blood from PD and control patients have further uncovered the role of oxidative stress in the pathogenesis of PD [161]. It is hoped that further integration of these techniques will yield a more comprehensive understanding of PD etiology and the biological pathways that mediate neurodegeneration which may eventually assist in developing more reliable biomarkers.

Conclusion

In spite of the efforts of biomedical researchers for two centuries little progress has been made in developing successful therapeutic strategies to PD. The critical limitation is that neuron is a post mitotic cell and by the time disease is diagnosed 60 to 70% of the neurons are degenerated. Therefore in order to develop therapeutic strategies it is important to develop methods to detect early dopaminergic neurodegeneration. Here lies the potential opportunity for biomedical researchers to take advantage of animal models and identify or characterize the strategies for early detection of PD pathology and apply this knowledge to understand the disease progression in human which is the ultimate goal of biomedical research. This will enable to work further either to delay the onset of neurodegeneration, if not to prevent death of DAn in PD.

Conflict of Interest

Authors declare no conflict of interest.

Acknowledgements

This work is partly supported by the Department of Biotechnology (DBT), Ministry of Science and Technology, India (R&D grant nos. BT/405/NE/U-Excel/2013 dated 11-12-2014 and BT/PR16868/NER/95/328/2015 dated 18-10-2016) to the corresponding author.

References

1. Kasap M, Akpinar G, Kanli. Proteomic studies associated with Parkinson's disease: Epert Rev Proteom. 2017;14(3):193-209.
2. Haaxma CA, Bloem BR, Borm GF, Oyem WJG, Leender KL, Eshies S, Booij J, Dluzen DE, Horstink MWM. Gender difference in parkinson's disease; J neunurosurgpsy. 2007;78(8):819- 824.
3. Sveinbjornsdottir S. "The clinical symptoms of Parkinson's disease. Journal of Neurochemistry. 2016;139:318–324. doi:10.1111/jnc.13691.
4. Manyam BV. Paralysis agitans and levodopa in "Ayurveda" Ancient Indian medical treatise. MovDisord.1990;5:47–48.
5. Zhang CZ. Ru Men Shi Qin. Ying Xu Zhai Edition. Bu Yue Lou Published in the 19th year of Jiajing Reign of the Ming Dynasty, Vol. 6,P1.
6. García RPJ. Prehistoria de la enfermed de Parkinson. [Prehistory of Parkinson's disease]. Neurologia (inSpanish). 2004;19(10):735–37. PMID15568171.
7. Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci. 2002 Spring;14(2):223-36; discussion 222. PMID: 11983801
8. Lees AJ. Unresolved issue relating to the shaking palsy on the celabration of James parkinson' 250th birth day. Mod. Disord. 2007;22(suppl 17):S327-34. Doi:10.1002/mds.21684.PMID18175393.
9. Calne DB, Langston JW. Aetiology of Parkinson's disease. Lancet. 1983;2(8365–8366):1457–1459.
10. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of melperidine analog, synthesis. Science. 1983;219:979–980.
11. Reeve A, Simcox E, Turnbull D. Ageing and Parkinson's disease: why is advancing age the biggest risk factor? Ageing Res Rev. 2014;14:19–30.

12. Calne DB, Langston JW. Aetiology of Parkinson's disease. Lancet. 1983;2(8365–8366):1457–1459.

13. Poewe W, Antonini A, Zijlmans JCM, Burkhard. Levodopa in the treatment of Parkinson's disease: an old drug still going strong. ClinInterv Aging. 2010;5:229–238.

14. Herrington TM, Cheng JJ, Eskandar E.N. Mechanisms of deep brain stimulation. J Neurophysiol. 2016; 115(1):19–38.

15. chaudhuri KR, Sauerbier A, Martinez Martin P. The burden of non motor symptoms in parkinsonsdi desase using a self completed non–motor questionnaire: A simple grading system. Scdirect. 2015;21(3):287-291.

16. Bergazo K, Tijero B, Eizaguirre AG, Sommee J, Lezcano E, Gabilondo I, Fernandez M, Zarranz JJ, Gomer E. Motor and nonmotorsymtoms of parkinson disease and their impact on quality of life and on different clinical subgroups, Neurolog. 2016;31(9):585-591.

17. Di Monte DA, MitraLavasani, Manning Bog AB. Environmental factors in Parkinson's disease. NeuroToxicology. 2002;23:487–502.

18. McCormack AL, Thiruchelvam M, Manning Bog AB, Thiffault C, et al. Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiol Dis. 2002;10:119–127.

19. Uversky VN. Neurotoxicant induced animal models of Parkinson's disease.understanding the role of rotenone, Maneb and paraquat in neurodegeneration. Cell Tissue Res. 2004;318:225–241.

20. Dhillon AS, Tarbutton GL, Levin JL, Plotkin GM, et al. Pesticide/environmental exposures and Parkinson's disease in East Texas. J Agromedicine. 2008;13:37–48.

21. Elbaz A, Clavel J, Rathouz PJ, Moisan F, et al. Professional exposure to pesticides and Parkinson disease. Ann Neurol. 2009;66:494–504.

22. Kamel F, Tanner C, Umbach D, Hoppin J, et al. Pesticide exposure and self reported Parkinson's disease in the agricultural health study. Am J Epidemiol. 2007;165:364–374.

23. Ritz BR, Manthripragada AD, Costello S, Lincoln SJ, et al. Dopamine transporter genetic variants and pesticides in Parkinson's disease. Environ Health Perspect. 2009;117:964–969.

24. Quadri M, Fang M, Picillo M, Olgiati S, Breedveld GJ, et al. Mutation in the SYNJ1 gene associated with autosomal recessive, early onset Parkinsonism. Hum Mutat. 2013;34:1208–1215.

25. Liu Z, Hamamichi S, Lee BD, et al. Inhibitors of LRRK2 kinase attenuate neurodegeneration and Parkinson like phenotypes in Caenorhabditis elegans and Drosophila Parkinson's disease models.HumMol Genet. 2011;20(20):3933–3942.

26. Uversky VN, Li J, Bower K, Fink AL. Synergistic effects of pesticides and metals on the fibrillation of alpha synuclein: implications for Parkinson's disease. Neurotoxicology. 2002;23(4–5):527–536.

27. Chiba K, Trevor AJ, Castagnoli Jr.N. Active uptake of MPP+, a metabolite of MPTP, by brain synaptosomes. BiochemBiophys. Res Commun. 1985;128: 1228–1232.

28. Javitch JA, D'Amato RJ, Strittmatter SM, Snyder SH. Parkinsonism inducing neurotoxin, N methyl 4 phenyl 1,2,3,6 tetrahydropyridine: uptake of the metabolite Nmethyl 4 phenylpyridine by dopamine neurons explains selective toxicity. Proc Natl AcadSci USA. 1985;82:2173–2177.

29. Daniels AJ, Reinhard Jr. JF. Energy driven uptake of the neurotoxin1 methyl 4phenylpyridinium into chromaffin granules via the catecholamine transporter. J Biol Chem. 1988;263:5034–5036.

30. Miller GW, Gainetdinov RR, Levey AI, Caron MG. Dopamine transporters and neuronal injury. Trends Pharmacol Sci. 1999;20:424–429.

31. Jeon BS, Jackson Lewis V, Burke RE. 6 Hydroxydopamine lesion of the rat substantia nigra: time course and morphology of cell death. Neurodegeneration. 1995;4:131–137.

32. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003;39:889–909.

33. Cicchetti F, Drouin Ouellet L, Gross RE. Environmental toxins and Parkinson's disease: what we have learned from pesticides induced animal models? Trends PharmacolSci. 2009; 30(9):475–483.

34. Wang XF, Li S, Chou AP, Bronstein JM. Inhibitory effects of pesticides on proteasome activity: implication in Parkinson's disease. Neurobiol Dis. 2006;23:198–205.

35. Olanow CW. The pathogenesis of cell death in Parkinson's disease. MovDisord.2007;22(17):335–342.

36. Shimizu K, Ohtaki K, Matsubara K, Aoyama K, et al. Carrier mediated processes in blood– brain barrier penetration and neural uptake of paraquat. Brain Res. 2001;906:135–142.

37. Miller GW: Paraquat. The red herring of Parkinson's disease research. Toxicol Sci. 2007;100:1–2.

38. Fei Q, McCormack AL, Di Monte DA, Ethell DW. Paraquat neurotoxicity is mediated by a Bak dependent mechanism. J Biol Chem. 2008;283: 3357–3364.

39. Barrientos A, Moraes CT. Titrating the effects of mitochondrial complex I impairment in the cell physiology. J Biol Chem. 1999;274:16188–1619.

40. Chauvin C, De Oliveira F, Ronot X, Mousseau M, et al. Ubiquinone analogs: a mitochondrial permeability transition pore dependent pathway to selective cell Death J Biol Chem. 2001;276:41394–41398.

41. Green DR, Reed JC. Mitochondria and apoptosis. Science. 1998;281:1309–1312.

42. Kroemer G, Reed JC. Mitochondrial control of cell death. Nat Med. 2000;6:513–519.

43. Wang X. The expanding role of mitochondria in apoptosis. Genes Dev. 2001;15:2922–2933.

44. Liu X, Kim CN, Yang J, Jemmerson R, Wang X. Induction of apoptotic program in cell free extracts: requirement for dATP and cytochrome c. Cell. 1996;86:147–157.

45. Du C, Fang M, Li Y, Li L, Wang X. *Smac,* a mitochondrial protein that promotes cytochrome c dependent caspase activation by eliminating IAP inhibition. Cell. 2000;102:33–42.

46. Verhagen AM, Ekert PG, Pakusch M, Silke J, Connolly LM, et al. Identification of DIABLO, a mammalian protein that promotes apoptosis by binding to and antagonizing IAP proteins. Cell. 2000;102:43–53

47. Li LY, Luo X, Wang X. Endonuclease G is an apoptotic DNase when released from mitochondria. Nature. 2001;412:95–99.

48. Susin SA, Lorenzo HK, Zamzami N, Marzo I, et al. Molecular characterization of mitochondrial apoptosis inducing factor. Nature. 1999;397:441–446.

49. Reed JC. Bcl 2 and the regulation of programmed cell death. J Cell Biol. 1994;124:1–6.

50. Reed JC. Double identity for proteins of the Bcl 2 family. Nature. 1997;387:773–776.

51. Zhang J, Fitsanakis VA, Gu G, Jing D. Manganese ethylene bis dithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. J Neurochem. 2003;84:336–346.

52. Fei Q, Ethell DW. Maneb potentiates paraquat neurotoxicity by inducing key Bcl 2 family members. J Neurochem. 2008;105:2091–2097.

53. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, et al. Occupational exposures to metals as risk factors for Parkinson's disease. Neurology. 1997;48:650–658.

54. Mergler D. Baldwin Early manifestations of manganese neurotoxicity in humans: an update. Environ Res. 1997;73:92–100.

55. Polymeropoulos M.H, Lavedan C, Leroy E, Ide S.E, Deheja A, Dutre A, Pike B, Root H, Rubenstein J, Boyer R et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Sci. 1997; 276,2045-4047.

56. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, and Shimizu N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998; 392,605-608.

57. Valente E.M, Abou-sleiman P.M, caputo V, Muqit M.M, Harvey K, Gispert S, Ali Z, Del Turco D, Bentivoglio A.R, Healy D.G, et al. Hereditary early onset Parkinson's disease caused by mutations in PINK1. Sci. 2004;304:1158-1160.

58. Paisan-Ruiz C, Jain S, Evans E.W, Gilks W.P, Simon J, Van Der Brug M, Lopez de Munian A, Aparicio S, Gil A.M, Khan N, et al. Cloning of the gene containing mutations that cause PARK8- link Parkinson's disease. Neuron . 2004;44:595-600.

59. Bonifati V, Rizzu P, Van Baren M.J, Schaap O, Breedveld G.J, Krieger E, Dekker M.C, Squitieri F, Ibanez P, JoosseMetal. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Sci. 2003;299:256-259.

60. Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid L.P, Goebel I, Mubaidin A.F, Wriekat A.L, Roeper J. et al. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat. Genet. 2006;38:1184-1191.

61. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralina T, Utra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Hardy KG. Synuclein locus triplication causes Parkinson's disease. Sci Aging Knowl. 2003; Environ. 44, or 23.

62. Olanow CW, Brundin P. Parkinson's disease and alpha synuclein is Parkinson's disease a prion –like disorder?.MovDisord. 2013; 28(1):31-40.

63. Parkinson J. An essay on the shaking palsy. 1817; Whitting hamand Rowland for Sherwood, Needly and Jones, London.

64. Charcot J-M. On Parkinson's disease. In Lectures on diseases of the nervous system delivered at the Salpeˆtrie're (transl. Sigerson G). 1877; 129–156. New Sydenham Society, London.

65. Charcot J-M. Vibratory therapeutics. The application of rapid and continuous vibrations to the treatment of certain diseases of the nervous system. J Nerv Ment Dis. 1892;19:880–886.

66. Gowers WR. Paralysis agitans. In A system of medicine (ed. Allbutt A, Rolleston T). 1899;156–178. Macmillan, London.

67. Christopher GG. The History of Parkinson's Disease, Early Clinical Descriptions and Neurological Therapies Cold Spring HarbPerspect Med. 2011;a008862.

68. Sushama AP, Onkar AA, Shripad NS, Jyoti PJ. Biological sources of L-DOPA: An alternative approach. Advances in Parkinson's Disease. 2013; 81-87.

69. Birkmayer W, Hornykiewicz O. Der L-Dioxyphenylalanin-Effektbei der Parkinson-kinese.WienKlinWschr. 1961;73:787–788.

70. Hornykiewicz O. Dopamine miracle: From brain homogenate to dopamine replacement. MovDisord. 2002;17:501–508.

71. Seo SY, Sharma VK, Sharma N, et al. Mush-room tyrosinase: Recent prospects. J of Agri and Food Chem. 2003;51:2837-2853.

72. Manyam BV. Paralysis agitans and levodopa in "Ayurveda": Ancient Indian medical treatise.

MovDisord. 1990;5:47–48.

73. Fahn S. The spectrum of levodopa-induced dyskinesias. Ann Neurol. 2000; 47(Suppl1):2–11.
74. Golbe LI. Young-onset Parkinson's disease: a clinical review. Neuro. 1991;41(2 Pt 1):168–173.
75. Forno LS. Neuropathology of Parkinson's disease. J NeuropatholExp Neurol. 1996;55(3):259–272.
76. Cotzias GC, Papavasiliou PS, Gellene R. L-dopa in parkinson'ssyndrome. N Engl J Med. 1969; 272.
77. Yahr MD, Duvoisin RC. Medical therapy of Parkinsonism. Mod Treat. 1968;283-300.
78. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45:651-60.
79. McIntyre CC, Hahn PJ. Network perspectives on the mechanisms of deep brain stimulation. Neurobiol Dis. 2010; 38:329–337.
80. May A, Bahra A, Büchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation incluster headache attacks. Lancet. 1998;352:275-8.
81. Wichmann T, DeLong MR, Guridi J, Obeso JA. Milestones in research on the pathophysiology of Parkinson's disease. MovDisord. 2011; 26:1032–1041.
82. Brown P, Mazzone P, Oliviero A, Altibrandi MG, Pilato F, Tonali PA, Di Lazzaro V. Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. Exp Neurol. 2004;188:480–490.
83. Lee JY, Kim HJ, Yun JY, Paek SH, Jeon BS. OFF-rebound dyskinesia in subthalamic nucleus stimulation in Parkinson disease. Can J Neurol Sci. 2011;38:768–771.
84. Sidtis JJ, Tagliati M, Alterman R, Sidtis D, Dhawan V, Eidelberg D. Therapeutic high- frequency stimulation of the subthalamic nucleus in Parkinson's disease produces global increases in cerebral blood flow. J Cereb Blood Flow Metab. 2012;32:41–49.
85. Vedam-Mai V, van Battum EY, Kamphuis W, Feenstra MGP, Denys D, Reynolds BA, Okun MS, Hol EM. Deep brain stimulation and the role of astrocytes.Mol Psychiatry. 2012;17:124–131.
86. Kringelbach ML, Jenkinson N, Owen SL, Aziz TZ. Translational principles of deep brain stimulation. Nat Rev Neurosci. 2007;8:623–635.
87. Zrinzo L, Foltynie T, Limousin P, Hariz MI. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J Neurosurg. 2012;16:84–94.
88. Pouratian N, Reames DL, Frysinger R, Elias WJ. Comprehensive analysis of risk factors for seizures after deep brain stimulation surgery. Clinical article. J Neurosurg. 2011;115:310–315.
89. Coley E, Farhadi R, Lewis S, Whittle IR. The incidence of seizures following deep brain stimulating electrode implantation for movement disorders, pain and psychiatric conditions. Br J Neurosurg. 2009;23:179–183.
90. Baizabal Carvallo JF, Simpson R, Jankovic J. Diagnosis and treatment of complications related to deep brainstimulation hardware. MovDisord. 2011;26:1398–1406.
91. Fenoy AJ, Simpson RK. Management of device-related wound complications in deep brain stimulation surgery. J Neurosurg. 2012;116:1324–1332.
92. Grill WM. Safety considerations for deep brain stimulation: review and analysis. Expert Rev Med Devices. 2005;2:409–420.
93. Okun MS. Deep-brain stimulation for Parkinson's disease. New Engl J Med. 2012;367:1529–1538.
94. Gubellini P, Salin P, Kerkerian-Le Goff L, Baunez C. Deep brain stimulation in neurological diseases and experimental models: from molecule to complex behavior. ProgNeurobiol. 2009;89:79–123.
95. Tsao R. Chemistry and Biochemistry of dietary polyphenols. Nutrients. 2010;2:1231-46.
96. Bureau G, Longpre F and Martinoli MG. Resveratrol and quercetin, two natural polyphenols,reduce apoptotic neuronal cell death induced by neuroinflammation. J Neurosci Res. 2008;86:403-410.
97. Jin F, Wu Q, Lu YF, Gong QH and Shi JS. Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats. Eur J Pharmacol. 2008;600:78-82.
98. Wight RD, Tull CA, Deel MW, Stroope BL, Eubanks AG, Chavis JA, Drew PD and Hensley LL. Resveratrol effects on astrocyte function: relevance to neurodegenerative diseases. Biochem Biophys Res Commun. 2012;426:112-115.
99. Lofrumento DD, Nicolardi G, Cianciulli A, De Nuccio F, La Pesa V, Carofiglio V, Dragone T, Calvello R and Panaro MA. Neuroprotective effects of resveratrol in an MPTP mouse model of Parkinson's-like disease: possible role of SOCS-1 in reducing pro-inflammatory responses. Innate Immun. 2014; 20:249-260.
100. Pallas M, Casadesus G, Smith MA, Coto-Montes A, Pelegri C, Vilaplana J and Camins A. Resveratrol and neurodegenerative diseases: activation of SIRT1 as the potential pathway towards neuroprotection. CurrNeurovasc Res. 2009;6:70-81.
101. Renaud J, Bournival J, Zottig X and Martinoli MG. Resveratrol protects DAergic PC12 cells from high glucose-induced oxidative stress and apoptosis: effect on p53 and GRP75 localization. Neurotox Res. 2014;25:110-123.
102. Bournival J, Quessy P and Martinoli MG. Protective effects of resveratrol and quercetin against MPP+ -induced oxidative stress act by modulating markers of apoptotic death in dopaminergic neurons. Cell Mol Neurobiol 2009;29:1169-1180.

103. Wu PF, Xie N, Zhang JJ, Guan XL, Zhou J, Long LH, Li YL, XiongQJ, Zeng JH, Wang F and Chen JG. Resveratrol preconditioning increases methionine sulfoxide reductases A expression and enhances resistance of human neuroblastoma cells to neurotoxins. J NutrBiochem. 2013;24:1070-1077.

104. Fuenzalida K, Quintanilla R, Ramos P, Piderit D, Fuentealba RA, Martinez G, Inestrosa NC and Bronfman M. Peroxisome proliferator-activated receptor gamma up-regulates the Bcl-2 anti-apoptotic protein in neurons and induces mitochondrial stabilization and protection against oxidative stress and apoptosis. J BiolChem. 2007; 282:37006-37015.

105. Wang J, Du XX, Jiang H and Xie JX. Curcumin attenuates 6-hydroxydopamine-induced Cytotoxicity by anti-oxidation and nuclear factor kappa B modulation in MES23.5 cells. BiochemPharmacol 2009;78:178-183.

106. Long J, Gao H, Sun L, Liu J and Zhao-Wilson X. Grape extract protects mitochondria from oxi dative damage and improves locomotor dysfunction and extends lifespan in a DrosophilaParkinson's disease model. Rejuvenation Res. 2009;12:321-331.

107. Ferretta A, Gaballo A, Tanzarella P, Piccoli C, Capitanio N, Nico B, Annese T, Di Paola M, Dell'aquila C, De Mari M, Aguirre JA, Korhonen L, Belluardo N and Lindholm D. Effect of resveratrol on mitochondrial function: implications in parkin-associated familiar Parkinson's disease. BiochimBiophysActa. 2014;1842:902-915.

108. Zhang F, Wang YY, Liu H, Lu YF, Wu Q, Liu J and Shi JS. Resveratrol Produces eurotrophic Effects on Cultured Dopaminergic Neurons through Prompting Astroglial BDNF and GDNF Release. Evid Based Complement Alternat Med. 2012; 2012:937605.

109. Chang CY, Choi DK, Lee DK, Hong YJ and Park EJ. Resveratrol confers protection against rotenone-induced neurotoxicity by modulating myeloper-oxidase levels in glial cells. PLoS One 2013; 8:e60654.

110. Ojha RP, Rastogi M, Devi BP, Agrawal A and Dubey GP. Neuroprotective effect of curcuminoids against inflammation-mediated dopaminergic neurode-generation in the MPTP model of Parkinson's disease. J NeuroimmunePharmacol. 2012;7:609-618.

111. Tripanichkul W and Jaroensuppaperch EO. Ameliorating effects of curcumin on 6-OHDA induced dopaminergic denervation, glial response, and SOD1 reduction in the striatum of hemiparkinsonian mice. Eur Rev Med PharmacolSci. 2013;17:1360-1368.

112. Tegenge MA, Rajbhandari L, Shrestha S, Mithal A, Hosmane S and Venkatesan A. Curcumin protects axons from degeneration in the setting of local neuroinflammation. ExpNeurol. 2014;253:102-110.

113. Chen J, Tang XQ, Zhi JL, Cui Y, Yu HM, Tang EH, Sun SN, Feng JQ and Chen PX. Curcumin protects PC12 cells against 1-methyl-4-phenylpyridinium ion-induced apoptosis by bcl-2- mitochondria- ROS-iNOS pathway. Apoptosis . 2006;11:943-953.

114. Wang MS, Boddapati S, Emadi S and Sierks MR. Curcumin reduces alpha-synuclein induced cytotoxicity in Parkinson's disease cell model. BMC Neurosci. 2010;11:57.

115. Pan J, Li H, Ma JF, Tan YY, Xiao Q, Ding JQ and Chen SD. Curcumin inhibition of JNKs prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease through suppressing mitochondria dysfunction. TranslNeurodegener . 2012;1:16.

116. Jaisin Y, Thampithak A, Meesarapee B, Ratanachamnong P, Suksamrarn A, Phivthong-Ngam L, Phumala-Morales N, Chongthammakun S, Govitrapong P and Sanvarinda Y. Curcumin I protects the dopaminergic cell line SH-SY5Y from 6-hydroxydopamine-induced neurotoxicity through attenuation of p53-mediated apoptosis. Neurosci Lett. 2011;489:192-196.

117. Jiang TF, Zhang YJ, Zhou HY, Wang HM, Tian LP, Liu J, Ding JQ and Chen SD. Curcumin ameliorates the neurodegenerative pathology in A53T alpha-synuclein cell model of Parkinson's disease through the downregulation of mTOR/p70S6K signaling and the recovery of macroautophagy. J Neuroimmune Pharmacol. 2013;8:356-369.tri.

118. Kim HT, Qiang W, Liu N, Scofield VL, Wong PK and Stoica G. Up-regulation of astrocyte cyclooxygenase- 2, CCAAT/enhancer-binding protein- homology protein, glucose-related protein 78, eukaryotic initiation factor 2 alpha, and c- Jun N-terminal kinase by a neurovirulent murine retrovirus. J Neurovirol. 2005;11:166-179.

119. Sawada H, Ibi M, Kihara T, Honda K, Nakamizo T, Kanki R, Nakanishi M, Sakka N, Akaike A and Shimohama S. Estradiol protects dopaminergic neurons in a MPP+ Parkinson's disease model. Neuropharmacology . 2002;42:1056-1064.

120. Wang J, Du XX, Jiang H and Xie JX. Curcumin attenuates 6-hydroxydopamine-induced cytotoxicity by anti-oxidation and nuclear factor kappa B modulation in MES23.5 cells. BiochemPharmacol. 2009;78:178-183.

121. Meesarapee B, Thampithak A, Jaisin Y, Sanvarinda P, Suksamrarn A, Tuchinda P, Morales NP and Sanvarinda Y. Curcumin I mediates neuroprotective effect through attenuation of quinoprotein formation, p-p38 MAPK expression, and caspase-3 activation in 6- hydroxydopamine treated SH-SY5Y cells. Phytother Res. 2014;28: 611-616.

122. Jagatha B, Mythri RB, Vali S and Bharath MM. Curcumin treatment alleviates the effects of glutathione depletion in vitro and in vivo: therapeutic implications for Parkinson's disease explained via in silico studies. Free RadicBiol Med. 2008;44:907-917.

123. Agrawal SS, Gullaiya S, Dubey V, Singh V, Kumar A, Nagar A and Tiwari P. Neurodegenerative Shielding by Curcumin and Its Derivatives on Brain Lesions Induced by 6- OHDA Model of Parkinson's Disease in Albino Wistar Rats. Cardiovasc Psychiatry Neurol 2012;2012:942981.

124. Liu Z, Yu Y, Li X, Ross CA and Smith WW. Curcumin protects against A53T alpha-synuclein induced toxicity in a PC12 inducible cell model for Parkinsonism. Pharmacol Res. 2011;63:439-444.

125. Beal MF. Therapeutic approaches to mitochondrial dysfunction in Parkinson's disease. Parkinsonism RelatDisord. 2009;15 Suppl 3:S189-194.

126. Zbarsky V, Datla KP, Parkar S, Rai DK, Aruoma OI and Dexter DT. Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. Free Radic Res. 2005; 39:1119-1125.

127. Ji HF, Shen L. The multiple pharmaceutical potential of curcumin in Parkinson's disease. CNS Neurol Disord Drug Targets. 2014;13:369-373.

128. Ono K, Hirohata M and Yamada M. Alpha-synuclein assembly as a therapeutic target of Parkinson's disease and related disorders. Curr Pharm Des. 2008; 14:3247-3266.

129. Singh PK, Kotia V, Ghosh D,Mohite GM, Kumar A and Maji SK. Curcumin modulates alpha synuclein aggregation and toxicity. ACS ChemNeurosci. 2013; 4:393-407.

130. Lee WH, Loo CY, Bebawy M, Luk F, Mason RS and Rohanizadeh R. Curcumin and its derivatives: their application in neuropharmacology and neuroscience in the 21st century. Curr Neuropharmacol. 2013; 11:338-378.

131. Liu Q, Kou JP and Yu BY. Ginsenoside Rg1 protects against hydrogen peroxide-induced cell death in PC12 cells via inhibiting NF-kappaB activation. Neurochem Int. 2011;58:119-125.

132. Lin WM, Zhang YM, Moldzio R and Rausch WD. Ginsenoside Rd attenuates neuroinflammation of dopaminergic cells in culture. J Neural TransmSuppl. 2007;72:105-112.

133. Park SM, Choi MS, Sohn NW and Shin JW. Ginsenoside Rg3 attenuates microglia activation following systemic lipopolysaccharide treatment in mice. Biol Pharm Bull. 2012;35:1546- 1552.

134. Chen XC, Zhu YG, Zhu LA, Huang C, Chen Y,ChenLM, Fang F, Zhou YC and Zhao CH. Ginsenoside Rg1 attenuates dopamine-induced apoptosis in PC12 cells by suppressing oxidative stress. Eur J Pharmacol. 2003;473:1-7.

135. Leung KW, Yung KK, MakNK, Chan YS, Fan TP and Wong RN. Neuroprotective effects of ginsenoside-Rg1 in primary nigral neurons against rotenone toxicity. Neuropharmacology. 2007;52:827-835.

136. Xu BB, Liu CQ, Gao X, Zhang WQ, Wang SW and Cao YL. Possible mechanisms of the protection of ginsenoside Re against MPTP-induced apoptosis in substantia nigra neurons of Parkinson's disease mouse model. J Asian Nat Prod Res. 2005;7:215-224.

137. Xu H, Jiang H, Wang J and Xie J. Rg1 protects iron-induced neurotoxicity through antioxidant and iron regulatory proteins in 6-OHDA-treated MES23.5 cells. J Cell Biochem. 2010;111:1537-1545.

138. Xu H, Jiang H, Wang J and Xie J. Rg1 protects the MPP+-treated MES23.5 cells via attenuating DMT1 up-regulation and cellular iron uptake. Neuropharmacology. 2010;58:488- 494.

139. Rudakewich M, Ba F and Benishin CG. Neurotrophic and neuroprotective actions of ginsenosidesRb(1) and Rg(1). Planta Med. 2001;67:533-537.

140. Schaneberg BT, Mikell JR, Bedir E, Khan IA. An improved HPLC method for quantitative determination of six triterpenes in Centellaasiatica extracts and commercial products. Pharmazie. 2003;58(6):381–384.

141. Mohamad A, Priyanka M, BovitoA,Muralidhara, and Sarat CY. Plant Products and Fermented Foodsas Nutrition and Medicine in Manipur State of Northeast India: Pharmacological Authenticity (Ed.) J. Purkayastha . In Bioprospecting of Indigenous Bioresources of North-East India. 2016;165-179.

142. SinghYR, DeviCO, AbujamSS, ChetiaD. Study on theethnomedicinalsystemofManipur. Int J Pharm Biol Arch. 2012a;3(3):587–591.

143. Singh E, Sharma S, Dwivedi J, Sharma S. Diversified potentials of Ocimum sanctum Linn (Tulsi): an exhaustive survey. J Nat Prod Plant Res. 2012b; 2:39–48.

144. Nalini K, Aroor AR, Karanth KS, Rao A. Effect of Centellaasiatica fresh leaf aqueous extract on learning and memory and biogenic amine turnover in albino rats. Fitoterapia. 1992;63:232–237.

145. Hazarika R, Singh AS, Neog B. Ethnomedicinal studies of common plants of Assam and Manipur. Int J Pharm BiolArch . 2012;3(4):809–815.

146. Gajare KA, Deshmukh AA, Pillai MM. Neroprotective effect of Bacopamonnierilinn. extract on lipofuscinogenesis and fluorescence product in brain of d-galactose induced ageing accelerated mice. J Cell Tissue Res. 2007;7(2):1167–1172.

147. Singh R, Sharma PK, Malviya R. Pharmacological properties and ayurvedic value of Indian buch plant (Acoruscalamus): a short review. Adv in Biol Res. 2011;5(3):145–154.

148. Nguyen HN, Byers B, Cord B, et al. LRRK2 mutant iPSC-derived DA neurons demonstrate increased susceptibility to oxidative stress. Cell Stem Cell. 2011;8:267–280.

149. Soldner F, Laganiere J, Cheng AW, et al. Generation of isogenic pluripotent stem cells differing

exclusively at two early onset Parkinson point mutations. Cell . 2011;146:318–331.

150. Sanchez-Danes A, Richaud-Patin Y, Carballo Carbajal I, et al. Disease-specific phenotypes in dopamine neurons from human iPS-based models of genetic and sporadic Parkinson's disease. EMBO Mol Med. 2012;4:380–395.
151. Mirakhori F, Zeynali B, Rassouli H, et al. Direct conversion of human fibroblasts into dopaminergic neural progenitor-like cells using TAT mediated protein transduction of recombinant factors. Biochem Biophys Res Commun. 2015;459:655–661.
152. Phetfong J, Supokawej A, Wattanapanitch M, et al. Cell type of origin inûuences iPSC generation and differentiation to cells of the hematoendothelial lineage. Cell Tissue Res. 2016;365:101–112.
153. Kyttala A, Moraghebi R, Valensisi C, et al. Genetic variability overrides the impact of parental cell type and determines iPSC differentiation potential. Stem Cell Reports. 2016;6:200–212.
154. Koch P, Breuer P, Peitz M, et al. Excitation induced ataxin-3 aggregation in neurons from patients with Machado–Joseph disease. Nature. 2011;480:543–546.
155. Ryan SD, Dolatabadi N, Chan SF, et al. Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1alpha transcription. Cell. 2013;155:1351–1364.
156. Gonzales KA, Ng HH. Looping around reprogramming: the topological memory of induced pluripotency. Cell Stem Cell. 2016;18:557–559.
157. Ji H, Zhang X, Oh S, et al. Dynamic transcriptional and epigenomic reprogramming from pediatric nasal epithelial cells to induced pluripotent stem cells. J Allergy Clin Immunol. 2015;135:236–244.
158. Schlossmacher MG, Mollenhauer B. Biomarker research in Parkinson'sdisease: objective measures needed for patient stratification in future causedirected trials. Biomark Med. 2010;4:647–650.
159. Sushil S, Carolyn SM, Azza K, Ali H, Anthony C, Comfort O, Miriana J, Yousef K, Manuchair E. Biomarkers in Parkinson's disease (recent update) Neurochemistry International 2013;63:201–229.
160. Berg D, Lang AE, Postuma RB, Maetzler W, Deuschl G, Gasser T, et al. Chang the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities. Lancet Neurol. 2013;12:514–24.
161. W Michael C, Theo K B, Yvonne L, Sheng P, and Jing Z. Using 'omics' to define pathogenesis and biomarkers of Parkinson's disease Expert Rev Neurother. 2010;10(6):925–942.