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Parkinson's Disease: An Overview

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Abstract

Parkinson's disease is an age associated chronic and neurodegenerative disease affecting 1% of the population over the age of 50 and 4-5% over the age of 85. The pathological hallmark of Parkinson's disease is progressive and selective loss of dopaminergic neurons in the substantia nigra pars compacta, causing dopamine deficiency in the brain and accumulation of Lewy bodies in the affected neurons. Clinical symptoms of Parkinson's disease include resting tremor, bradykinesia, rigidity, and postural instability. Non-motor symptoms such as sleep disorder, olfactory impairment, constipation and neuropsychiatrics are manifested many years before the onset of motor symptoms. Environmental toxins such as paraquat and rotenone cause sporadic Parkinson's disease while genetic mutations cause familial Parkinson's disease. Therapy of Parkinson's disease is divided into 140 years before dopamine and 50 years of dopamine era. 140 years before dopamine includes venesection, vibratory therapy, hydrotherapy, spa treatment and 50 years of dopamine era includes L-dopa and deep brain stimulation. Drosophila model of Parkinson's disease has been a great use to screen natural products with anti-oxidant and anti-inflammatory properties to decipher their neuroprotective efficacy with an aim to develop therapeutic molecules for Parkinson disease in humans. To understand pathways leading to death of dopaminergic neurons and to prevent it remains a challenge and opportunity for all the biochemical researchers.

Key words: Alpha-synuclien, Lewy bodies, dopamine, levodopa, curcumin, resting tremor, bradykinesia, shaking palsy, antioxidant, anti-inflammatory, Parkinson's disease.

Introduction

Parkinson's disease (PD) is the second most common age associated chronic and progressive neurodegenerative disorder after Alzheimer disease affecting approximately 1% of population above the age 50 and 4-5% of the population above the age of 85[1, 2]. The well known pathology of PD is the progressive and selective loss of dopaminergic neurons (DAn) in the substantia nigra pars compacta (SNpc), causing a deficiency of brain dopamine (DA) content. The low dopamine content in the brain DAn gives rise to motor defects (Symptoms) such as muscle rigidity, bradykinesia, postural instability and resting tremor. The motor symptoms are collectively called "Parkinsonism or Parkinsonian syndrome"[3, 4]. Another pathological hallmark of PD is the presence of the cytoplasmic inclusions called lewy bodies in the brain DAn. Lewy bodies are mainly composed of alpha- synuclein (α-syn) and ubiquitin among other proteins[4]. A numerous non-motor

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symptoms (NMS) are considered to be an integral part of the disease and there is strong evidence that some of the symptoms such as hyposmia, olfactory dysfunction, constipation, sleep behavioral disorder, rapid eye movement etc are manifested much earlier than any of the motor symptoms occurring in the patient[5].

In spite of intensive and extensive studies carried out worldwide, the etiology of PD remains generally unknown. Aging remains the major risk factor even though both genetic components and exposure to environmental toxins, such as paraquat (herbicides) and rotenone (pesticides) and heavy metals, are thought to play a crucial role in onset of the disease [6]. 90% to 95% PD cases are believed to have caused by sporadic components. Studies show that environmental toxins may be more important than that of the genetic factors in familial aggregation of PD. In majority of the PD patients, the cause is environmental influence, probably toxins, and sustained neuronal loss due to advancing age[7]. Observing PD in 1-methyl 4-phenyl 1, 2, 3, 6-tetrahydropyridine (MPTP) drug user's reinvented curiosity in reexamining environmental influences[8].

Available treatments for PD mitigate only symptoms of PD but can't cure and slow down the progress of the disease. Levodopa (L-dopa) is a precursor of dopamine. Although it is the leading treatment of PD for 50 years, it improves symptoms only by the replacement of dopamine, with variable efficacy and various side effects. L-dopa improves motor defects by enhancing DA levels of the brain neurons[9]. However, chronic use of L-dopa causes dyskinesia (a type of movement disorders, characterized by involuntary muscle movement) that weakens the benefits of L-dopa. When the drugs are ineffective, Surgery has been used to reduce motor symptoms in advance cases[10]. Pathology of PD is believed to have affected by several pathways, hence the development of effective treatment for PD is difficult. Due to poor knowledge of the molecular mechanism(s) of the pathology, there are no cure and preventive intervention.

History

The Indian traditional texts "Ayurved" from about 1000 BC provide descriptions that suggest the treatment of diseases which resemble to PD[11]. Many other sources, such as Egyptian papyrus, the Bible and Galen's writings describe symptoms which are similar to PD[12]. After Galen's writing, no references which are unambiguously related to PD are found until 17th century[12]. In 18th century, many authors including Chomel, Hunter, and Sylvius, Gaubius, wrote about the elements of PD[13, 14].

Much later in 1817, "200th anniversary of shaking palsy", James Parkinson (1775-1824), a general medical practitioner who worked in shore ditch, published his famous work "An Essay of the shaking palsy". The essay for the first time described its signs and symptoms, individual case observations on 6 subjects, differential diagnosis, etiology and contemporary treatment[15]. Other Neurologists like Erb, Trousseau, Kinnier, and Gower had contributed for understanding of the PD and Jean-Martin Charcot, later, recognized the importance of James Parkinson's essay on shaking palsy and named the disease after him[16]. Charcot contributed extensive details to Parkinson's observation and included bradykinesia and rigidity as a important diagnostic features of the disease[15].

Clinical Features

1. Motor Symptoms:

PD is clinically characterized by the motor defects. Motor symptoms (MS) involve a loss of motor coordination or causing restricted mobility. MS includes resting tremor, rigidity, bradykinesia, and postural instability.

Resting Tremor: Approximately 75% of patients experience a slight shaking either in the hand or in the legs or less commonly in the face in the early

stages of the PD. The resting tremor includes shaking or oscillating movement, and normally occurring while the affected body parts are at rest or unemployed, therefore called it "resting tremor. A normal onset of PD is shaking in one finger", the affected body part shakes while it is not performing any function. When the hand is folded or when the hand is held loosely at the side, the fingers or the hand will tremble.

Rigidity: The stiffness and inflexibility of the limbs, neck and trunk are known as rigidity. A person with rigidity is not swinging his or her arms while walking. Muscles usually stretch when they relax and then move. The muscle tone of an affected body part remains stretch and does not relax, contributing to a decreased range of motion. Patients normally experience stiffness of the neck, shoulder and leg. It can be uncomfortable or even painful.

Bradykinesia: It is a "slow movement" which explains about the reduction of spontaneous movement. This gives the appearance of abnormal stillness and causes a reduction in facial expression. Owing to bradykinesia, patients usually have problems performing everyday functions, such as eating food, buttoning a shirt or brushing his or her teeth. Patients who experience it may walk with shuffling and short steps. Bradykinesia makes difficulty with repetitive motion, such as finger tapping. It may affect patient's speech as well, which may become either faster or less clear as disease advances.

Postural Instability: Patient with postural instability can't maintain upright posture, because he/she has lost some of the reflexes required for maintaining an upright posture, and may bend backwards if pushed slightly and may result in a backwards fall. Patients with postural instability may face problems particularly when making turns or quick movements. Postural stability is tested by using the "pull test." Some patients developed an uneasy tendency to fall backward when getting up from sitting position, or turning.

2 Non Motor Symptoms (NMS)

NMS are manifested many years before the onset of motor symptoms in the PD patients. NMS do not involve motor coordination of the central nervous system and are commonly prevalent in a large population of Patients. NMS include sleep disorder, neuropsychiatric, sensory symptoms, autonomic dysfunctions, gastrointestinal symptoms. Other symptoms include olfactory, REM, constipation[17]. Some of these symptoms appear at the early stage of the disease and remain throughout the course of the disease and are included in the clinical diagnosis of PD.

Contemporary Ideas

The present understanding of the PD are decoded from the intensive research conducted worldwide. The year 2017 marks the 20th anniversary of the discovery of the first gene that induces monogenetic form of PD which is α- syn[18]. However, only 5% - 10% of the PD cased is attributed to genetic cause (Familial PD) and 90% -95% of the PD cases is attributed to environmental toxin cause (sporadic PD).

Depletion of DA and degeneration of the nigrostriatal pathway have been identified as causative of the motor symptoms of PD. The first evidence that dysfunction of mitochondria causes the cellular etiology of PD arises from studies of MPTP. The MPP^+ (1-methyl-4-phenylpyridinium), the toxic metabolite of MPTP, blocks complex I of the mitochondrial electron transport chain[8]. In the following years, a defect of complex I was discovered in the SN of PD patients[19]. Mitochondrial complex I defects induce progressive degeneration of DAn. Conformational changes in complex I owing to deficiency of apoptosis inducing factor do not lead to neurodegeneration caused by the loss of DAn, but make the DAn more sensitive to neurotoxins[20]. Several studies have shown that mitochondrial dysfunction causes chronic

production of reactive oxygen species (ROS) and leads to death of DAn. Superoxides are produced by the mitochondrial complex I in the electron transport chain weather toxin is present or absence. Brain postmortem samples of PD patients have shown evidences of oxidative damage[21]. Many other theories have been proposed for the pathogenesis of PD, of which, dysfunction of mitochondria plays a pivotal role in both sporadic and genetic forms of the disease. Selective dysfunction and the death of DAn are considered to be caused by both iron toxicity in the SN and oxidative stress (OS)[22].

1 Genetic Mutations and PD

α- syn gene (SNCA) is the main component of Lewy bodies. SNCA is the most intensively and extensively investigated PD gene with respect to causative mutations, function of the gene and the encoded proteins. The mutation in SNCA appears to be unique when compared with other PD inducing genes. SNCA triplicate carriers have a more complicated phenotype and faster progression than duplicate carriers. SNCA triplicate carrier has about a 15 years earlier onset than duplicate carrier. Other disease related genes (LRRK2, GBA) have also been linked to alteration of SNCA levels[23]. The presence of Lewy body will be a necessary requirement for diagnosis of PD; however Lewy bodies occur in the central nervous system in other disease conditions too.

The most common pathogenic changes that is linked to autosomal dominant PD are the mutations in LRRK2 [24; 25]. The phenotype of Idiopathic PD is indistinguishable from that of LRRK2 p.G2019S mutations. LRRK2 has a guanosine-5-triphosphate that regulates serine/threonine kinase activity of pathogenic LRRK2 variants. These pathogenic variants are increasing autophosphorylation or kinase activity, raising the potential not only for a mechanistic understanding of the effect of LRRK2 mutations but also for the development of biomarkers and of LRRK2 kinase inhibitors as a causal therapeutic target.

Parkin is one of the most commonly affected PD genes. Phenotypes such as defects in wing position, locomotive defects, DA neurodegeneration[26] are shown by the parkin fly mutants. These mutant flies have swelling mitochondria in their flight muscles and sperm, suggesting that mitochondrial dysfunction is an important cause of PD. Finding of mitochondrial defect in the parkin mutants is unusual because various parkin substrates identified before were localized in the cytoplasm. Hence substrate accumulation due to loss of parkin may have caused ER stress and thereby result in death of the DA neurons[27].

DJ-1 appears to protect cell against OS. DJ-1 mutant flies show locomotive defects indicating that DJ-1 is involved in protecting the cell against OS[28].

PINK1 has serine/ threonine kinase domain. This kinase activity is essential for protection of the disease. Since the phenotypes of PINK1 fly mutants are similar with phenotypes of parkin mutants[29], it leads to the prediction that these two genes act in a common pathway. Subsequent studies have shown that over expression of parkin suppressed the phenotypes of PINK1 mutants[29]. This finding shows that parkin and PINK1 are related in the protection of mitochondrial integrity and function. It also suggested that PINK1 and parkin linked PD pathogenesis is the key cause of mitochondrial dysfunction.

Therapy:

1. 140 Years before DA

The treatments before L-dopa include venesection, vibratory therapy, solanaceous alkaloids, hydrotherapy, spa treatments and light exercise. Venesection is specifically removing blood from the neck, followed by vesicatories to induce

inflammation of the skin[30]. The therapy was designed to remove blood and inflammatory pressure from the spinal cord and brain, which shrink the medulla that Parkinson considered the site of neurological dysfunction. In 1867, Jean Martin Charcot recommended solanaceous alkaloids to the PD patients and became popular therapy for about 75 years[31] and he recommended vibratory therapy too for the treatment of PD where he developed a device to provide rhythmic movement by an electrically powered "shaking chair"[32]. Gower used morphia, arsenic, hyoscyamine, conium (hemlock), and cannabis "Indian hemp" as effective natural products for temporary decline in resting tremor.In 1950s, synthetic drugs and stereotactic neurosurgery became the standard medical therapy for PD and were used until Cotzias showed the remarkable benefit from L-dopa[33].

2. DOPAMINE ERA, 50 YEARS

In 1957, a simple experiment was performed by Carlsson and colleagues[34] showing that L-dopa reversed the reserpine induced Parkinsonian state in rabbits. In 1958, Carlsson strongly believed that DA was present in brain[36]. The distribution of DA was mapped out in the brain of animals[36] and humans[37] in the following year. In 1958, Carlsson, presented a paper at the international catecholamine symposium, suggested that PD was related to brain DA[38]. In 1960, Hornykiewicz found a neostriatal DA deficiency in both PD and postencephalitic Parkinsonism[39]. Thus began the era of DA. Nobel Prize in physiology and medicine for the year 2000 was awarded to Carlsson for his contributions to the treatment of PD[40].

With the understanding that the natural precursor to DA was L-dopa, Hornykiewicz's supply of laboratory supplied L-dopa to Birkmayer who injected it intravenously for the first time to PD patients in 1961. It was observed that, severely affected patients who could not sit up, patients who could not stand up after sitting, and patients who could not start walking when standing performed all these activities with ease after taking L-dopa. Patients could walk around normally and could even play games[41]. Studies had found L-dopa containing compounds in early medicine. A naturally occurring amino acid is present in L-dopa. The enzyme immobilization technique was commercially used to synthesize L-dopa from mushroom tyrosinase[42]. This technique is very useful for the production of L-dopa because it reduces the cost of production due to the reusability of the enzymes.

2.1 L-DOPA:

Since L-dopa can cross blood brain barrier (BBB) and precursor to DA, L-dopa is used in place of DA, as DA cannot cross the BBB, for the treatment of PD. It is given either intravenously or orally where it gets converted to DA before it crosses BBB. Therefore it needs to be administered with a substance called carbidopa (decarboxylase inhibitor) to decrease the required amount of L-dopa and to ameliorate some of its side effects such as nausea and vomiting by decreasing the supply of free DA outside the brain. Carbidopa delays the conversion of L-dopa into DA until it crosses the BBB and preventing some of the side effects that often accompany L-dopa treatment. L-dopa is a leading therapeutic drug which reduces the motor features and other symptoms of the disease in the initial stages of the disease. The absorption of L-dopa can be interfered by high protein content diet, so patients are restricted in consuming high protein content diet during the initial stages of the therapy[43].

Limitations

L-dopa-induced dyskinesia, an abnormal involuntary movement, is caused by prolonged used of L-dopa. These are uncontrolled and repetitive movement in the legs, arms, axis, and oro-facial zone[44]. Approximately 55% of L-dopa-treated patients who get treatment with the drug for more than 5

years, in about 85% of patients who use the drug for 10 years, and in almost all patients with young onset disease experienced L-dopa induced dyskinesia[45]. Patients, who received the drug for long time, usually suffer from a variety of side effects such as vomiting, nausea, and low blood pressure. A serious concern is that hallucinations and psychosis are caused by long term treatment of the drug. Low doses L-dopa cause serious dyskinesia to the patients immediately after taking the drug. Since L-dopa itself is a pro-oxidant which could cause cell damage due to oxidative stress in PD and other neurological related disorders, long term used of L-dopa is very harmful. A serious problem in the treatment of L-dopa is that, it is harmful to DAn. These conditions have not yet been proven by the clinical trials.

3. Deep Brain Stimulation (DBS)

DBS is a device to treat movement disorder such as PD. It inactivates the area of the brain where electrical impulses that cause the symptoms of PD and its related symptoms are generated. Structural neuroimagings such as magnetic resonance imaging or computed topography are used to choose the target location in the brain. Sub thalamic nucleus (STN) and Globus pallidusinterna of the mid brain are the target location of DBS device. Identification of target location is very important. Once identified, permanent electrodes are placed in the thalamus (to treat tremor), in the globuspallidus and sub thalamic nucleus (for PD). These electrodes are connected by wires to a type of pacemaker device called an impulse generator (IPG) implanted below the skin of the chest, below the collarbone[46]. The IPG can easily be programmed using a computer that sends radio signals to the device. Patients are provided special magnets or other devices to externally turn the IPG on or off. Once activated, continuous electrical signals to the target areas in the brain are sent by the device, blocking the signals that cause tremors and other symptoms of PD. DBS has the same effect as thalamotomy or pallidotomy surgeries without actually destroying parts of the brain[47]. It changes the rate of signal and pattern of individual neurons in the basal ganglia[48] and abnormal rhythmic oscillation between the cortex and the basal ganglia are removed by DBS[49].The electrical signal stimulates synapses of the target neurons to release neurotransmitters and excites surrounding astrocytes to release calcium from the efferent neurons[50].

Although DBS is a useful device for the treatment of movement disorders, it depends on a number of parameters, such as stimulation, structural configuration of the electrode, physiological properties of the targeted cells, and the surrounding tissue, and possibly the fundamental pathophysiology of different disease states. However, it may take many months until the simulators and medications are adjusted sufficiently for patients to receive adequate symptom relief. But, overall, DBS induces few side effects[51]. DBS was developed in the dopamine era and has been quite effective in mitigating motor complications [52].

Limitations

The most adverse disadvantage associated with placement of leads for DBS are infection and intracranial hemorrhage. It also includes accurate neurological and neuropsychological complications such as surgery and stimulation and was found that the overall incidence of hemorrhage was 2.6% of patients and hemorrhage resulting in lack of permanent neurological activities or death in 1.1%[53]. Post surgery seizures have also been reported and usually occur within 48 hrs of surgery[54] with an estimated incidence of 2.4%[55]. The most common hardware complications include misplacements of the electrodes, infections, migrations, wire fractures, device malfunction and skin erosion[56] which often requires cleaning of the device and a period of antibiotic treatment before consideration for device replacement[57].

Impulse-related side effects include tremor, dyskinesia, muscle contractions, dysarthria, ocular deviations, headache, pain and paresthesia[58]. Verbal fluency is the most common cognitive adverse effect of STN DBS, caused by surgical electrode implantation rather than stimulation-induced interference[59]. In general, DBS is a comparatively safe approach associated with low rate of side effects, which is an effective therapeutic option to assist in a multitude of neurological diseases.

4. Natural Remedies To Parkinson's Disease

Drosophila model of PD has been a great use to screen natural products with anti-oxidant and anti-inflammatory properties to decipher their neuroprotective efficacy with an aim to develop therapeutic molecules for PD in humans.

Some of the studies are as following:

a) *Mucuna pruriens: M. pruriens,* commonly known as Cow Hedge plant or Velvet Bean and Atmagupta in India is a climbing leguminous plant belonging to the Fabaceae family and is believed to be originated from southern China and eastern India[60]. L-dopa was found to be naturally present in the seed of *M. pruriens*[61,62] with an approximate of 4 to 6% concentration[63]. *M. pruriens* has been shown to have anti-parkinson and neuroprotective affects wherein the motor deficit, olfactory, mitochondrial and synaptic impairment were rescued in *Drosophila* model of PD[64]. Antioxidant and metal chelating activity were also reported in animal model of PD[65]. Nicotine adenine dinucleotide (NADH) and coenzyme Q-10 which are shown to have a therapeutic benefit in PD due to their ability to escalate mitochondrial respiration and antioxidant proficiency, were present significantly in the *M. pruriens* cotyledon powder, assisting the neurorestorative effect of *M. pruriens*[66].

b) *Withania somnifera*: *W. somnifera* popularly known as Ashwagandha or Indian Ginseng or Winter Cherry[67,68] is a green shrub from Solanaceae family[69]. It is reported that the root extract significantly reduced the lipid peroxidation[70] and increased the superoxide dismutase (SOD) and catalase activity, possessing a free radical scavenging property[71]. The action of regulation on GABAergic, cholinergic and oxidative systems was due to the phytochemicals present in the plant[72,73]. *W. somnifera* extract rescued the locomotor deficits, oxidative impairments and neurotoxicity in rotenone-induced *Drosophila* fly model[74]. Also studies on PD animal models have shown *W. somnifera* as a potential drug in treating catecholamines[75,76], oxidative damage[76] and its effect on the apoptotic pathways[76].

c) Curcumin: Curcumin, a natural phenolic compound isolated from the roots of *Curcuma longa* belongs to the family of Zingiberaceae. Curcumin possess anti-inflammatory, antioxidant, anti-carcinogenic, and wound-healing effects[77-79]. Neuroprotective efficacy of curcumin was shown in a phase specific manner in *Drosophila* model of idiopathic PD[80]. A dose dependent delay in the loss of activity pattern, reduction in the OS and apoptosis with increase in the life span of PD model flies with curcumin was observed[81].

d) Resveratol: A natural phenol found in red grapes, mulberries, peanuts, wines, and tea[82] possess antioxidant and free radical scavenger activity due to its ability to transfer hydrogen atoms or electrons to the free radicals[83,84]. Resveratol was shown to have a positive effect on lifespan of *Drosophila melanogaster*[85] by modulating the genetic pathways that reduce the cellular damage[86].

e) Coffee: Coffee is shown to have neuroprotective effect in fly PD models and presence of nuclear factor-2 (Nrf2)-activating compounds in coffee account for the reduced risk of PD[87]. Caffeine one of the main component of coffee, is widely used as a psychotropic substance and its neuroprotective function is credited to its antagonistic action on adenosine 2A (A_{2A}) receptors in the brain[88]. Study on MPTP induce mouse model of PD shows the neuroprotective effect of caffeine on striatal DA and DA transporter binding sites by blocking the A_{2A} receptors[89].

f) Tobacco: Tobacco is shown to have neuroprotective effect in the degeneration of DAn in the fly PD models through an NRF2-Dependent Mechanism. Nicotine, one of the active ingredients of tobacco, increases lifespan and rescues olfactory and motor deficits in a *Drosophila* model of PD[90].

g) *Bacopa monnieri*: *B. monnieri* showed neuroprotective properties against rotenone induced oxidative damage and neurotoxicity in *Drosophila* model of PD [91] and improved climbing ability in PINK1 mutants PD fly model[92].

h) *Centella asiatica*: *C. asiatica* leaf extract was shown to reduce the PD symptoms in transgenic *Drosophila* model of PD. Exposure of PD fly model to *C. asiatica* resulted in significant delay in loss of motor deficit and reduced the OS in the brain[93].

i) *Eucalyptus citriodora: E. citriodora* extract showed a dose dependent significant delay in the loss of climbing ability and reduction in the oxidative stress in the brain of PD model flies[94].

j) Epicatechin Gallate (EG): EG showed a dose-dependent significant delay in the loss of climbing ability and reduced the OS and apoptosis in the brain of *Drosophila* PD model[95].

k) Nordihydroguaiaretic Acid (NDGA): NDGA, a potent anti-oxidant compound of crosote bush (*Larreatridentata*) were reported to possess antigenotoxic, antineoplastic, anti-viral, and anti-inflammatory properties[96] and showed dose dependent delay in the climbing disability of PD model flies[97].

l) *Ginkgo biloba*: *Ginkgo biloba* extract 761 was shown to have neuroprotective and antioxidant effect against the damage to brain[98], prevent OS[99] and also reduce the locomotors[100] and behavioural deficit[101] caused by the neurotoxin in PD animal model.

m) Vitamins: Vitamin E (alpha-tocopherol) was shown to have an antioxidant effect on the lifespan of PD fly model under hyperoxia condition[102]. L-Ascorbic acid treatment in a dose dependent significant delay the loss of climbing ability of PD model flies[103].

n) Regrapex-R: Regrapex-R prepared from whole grape (*Vitis vinifera*) and *Polygonum cuspidatum* protects mitochondria from oxidative damage and improves locomotors dysfunction and extends lifespan in *Drosophila* PD model[104].

o) Celastrol: A potent anti-inflammatory and antioxidant triterpene extracted from the root bark of *Tripterygium wilfordii* contains therapeutically active compounds such as terpenoids, alkaloids, and steroids[105]. In *Drosophila* using the DJ-1αRNAi PD model, celastrol protected the neurodegeneration of DA neurons and DA level and showed neuroprotective effect in locomotors activity and oxidative stress[106]. As shown also in the MPTP-injected mouse model of PD, celastrol significantly reduced the DA neuron loss in the SNpc and the dimunition of striatal dopamine induced by MPTP[107].

p) *Decalepis hamiltonii* (Dh): Dh also known as swallow root was shown to protect against paraquatsensitivity in α-syn transgenic flies and delayed the onset of PD-like symptoms by suppression of OS[108].

q) Tangeritin: Tangeritin a flavone found in the peels of Mandarin oranges (*Citrus reticulata*) delays the loss of climbing ability and increases the DA content and also reduces the OS markers in transgenic *Drosophila* model of PD[109].

r) Geraniol (GE): GE, an acyclic monoterpene alcohol found in lemongrass and aromatic herb oils[110] significantly delays the loss of locomotors ability and reduces the OS in the brain of PD fly model[111].

s) *Ocimum sanctum: O. sanctum* known as Tulsi, extract of which showed a dose-dependent significant delay in the loss of climbing ability and reduction in OS in the brain of PD model flies[112].

t) *Selaginella delicatula*: *S. delicatula* a pteridophyte, aqueous extract showed antioxidant activity in rotenone induced PD fly model by attenuating the locomotors deficits and also restoring the antioxidant enzyme[113].

u) *Valeriana officinalis: V. officinalis*, a hardy perennial flowering plant treatment to *Drosophila* model of PD offered protection against the mobility defect and normalized the antioxidant enzymes expression induced by rotenone[114].

v) Cinnamon extract: Cinnamon extract When administered to *Drosophila* fly model expressing mutant A53T α-syn in the nervous system, show significant positive effect on the behavioral symptoms of the flies and on α-syn aggregation in the brain[115].

Future Challenges and Oppurtunities

PD is believed to be caused by several pathways which are poorly understood despite studies on various PD models being conducted worldwide. To understand pathways leading to death of DA neurons and to prevent it remains a challenge and opportunity for all the biochemical researchers. Studies on intracellular calcium homeostasis, α- syn, whole genome sequencing, mitochondrial dysfunction, and protein misfolding may unlock the key to understand the pathways leading to death of DAn.

Intracellular calcium homeostasis of DAn in the SN is required not only for dopamine release, but also regulates their lysosomal and mitochondrial activities, OS levels and vulnerability to degeration in PD [116]. It is also important for mitochondrial, iron homeostasis[117] and the kinase of mitochondrial PINK1 factors in PD. Another important point for the future of the PD is whole genome sequencing. The whole-exome and whole-genome sequencing technologies promise a new wave of genetic discoveries for PD, especially in the area of rare variants of intermediate penetrance (like LRRK2-G2019S or the GBA variants), that was not detected in the previous genome wide approaches, but might represent a relevant missing piece in the complex etiological area of PD. The role of epigenetic modifications, genomic regulation of gene expression and chromatin modifications in the pathogenesis of PD represent other exciting areas of future explorations, enabled by the novel generations of sequencing technologies [15]. Systematic and comprehensive accounts of phenotypic data of patients with monogenic PD are currently lagging behind the advances in PD genetics and challenge an important unmet need for successful translational efforts. In this context, it is important that newly detected PD genes and as yet unconfirmed one's need to undergo careful independent validation before being added to diagnostic PD gene panels. Detailed pathogenetic

understanding of the known PD genes and proteins will be key for the development of causative treatment strategies and possible exploitation of mechanisms of endogenous disease protection as suggested by reduced penetrance of many PD gene mutations[15].

Conclusion

Despite considerable understanding of the pathology of the disease over the last 200 years since the publication of the "shaking palsy" various complicated symptoms of PD still remain a challenge for the patients who are treated with L-dopa or with DBS. Till now, no drug or surgery is available to cure or slow down the progress of the disease rather than acting on symptoms. Here in lies the great opportunity to budding biomedical researchers.

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Conflict of interest

Authors declare no conflict of interest

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