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Review Article

The Invertebrates and Their Role Parkinson's Disease Therapy

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Abstract

Neurodegenerative diseases are becoming increasingly common as life expectancy increases. After Alzheimer's Disease (AD), Parkinson's Disease (PD) is the second most prevalent and incidental neurodegenerative disorder commonly affecting more than 2% of the elderly population of age 65. Because of the destructive consequences of PD and insufficient current management strategies, it is essential to develop an effective suite of preventative regimens and treatments. The main hurdle in the development of neuroprotective therapies for PD is the limited understanding of the key molecular mechanisms. The search for cardinal hallmarks, potential therapeutics and preclinical animal models are in progress. Examining therapeutic compounds and molecular pathways in human and animal models are limited due to high cost, ethical concerns and lengthy time frame. Invertebrate models are the best alternative in terms of cost, ethical concerns and time frame and up to some extent provided basic insight into the disease pathogenesis. In this review, we discuss the invertebrate models possibilities for gaining insight into the basic molecular mechanisms and pathways involved in PD pathogenesis as well as the screening of the potential therapeutic and neuroprotective compounds.

Keywords: Parkinson's disease; *Planaria; Tribolium castaneum; Drosophila melanogaster; Caenorhabditis elegans*

Introduction

Parkinson's Disease (PD) is a geriatric neurodegenerative disorder second only to Alzheimer's disease in prevalence [1,2]. PD was first termed by James Parkinson as "shaking palsy", later termed as "Parkinson" by Jean-Martin Charcot [3,4]. Before James Parkinson, Zihe Zhang (1151-1231) of the Jin-Yuan Dynasty describes some similar disease manifestations as that of PD [5]. In 1997 scientist discovered that SNCA is the prime protein in LB [6]. Recently cell-to-cell transmission of SNCA has been identified [7]. Clinical-pathological hallmarks of PD are dopaminergic neuronal loss in SNpc of the midbrain and intracellular SNCA accumulation. PD is characterized by both motor as well as non-motor impairment. Motor impairment manifestations are resting tremor, rigidity, postural imbalance, slowness of movement and freezing of gait [8,9]. While non-motor impairment manifestations include dementia, sleep disturbances, anxiety, apathy, constipation, and depression [10,11]. PD prevalence is associated with age as demonstrated by meta-analysis, like 1% at 65 and 5% at 85, as well as gender, like the male has a high ratio of disease prevalence as compared to female [9,12,13]. A major breakthrough in PD research occurred in 1997 with the discovery of SNCA genes mutation which is the main cause of the familial form of PD [14,15]. Along with these discoveries, the epidemiological studies strengthen the fact that both genetic and environmental factors increase the risks of PD prevalence [16,17]. To date, there is no known drug, which can completely eradicate the root cause of the PD. All the currently available medications and therapies provide symptomatic relief (Table 1). In order to eradicate the root causes of the disease, scientists are conducting different kinds of researches in order to discover potent and novel drugs for the permanent treatment of PD and for this, they are using different experimental tools and disease models to get the ultimate effective results. Different disease models including both vertebrates and invertebrates have been using by different researchers and each model has its own capability of covering different technical aspects of the disease. Vertebrates including Rodents and Primates are closest in regards to human anatomy and these disease models have revealed key points and molecular pathways involved in PD progression regarding impacts of environmental toxins, age and genetic mutation on the disease fate. However, these vertebrate's models have some limitations in the context of ethical concerns, high-throughput screening approaches for detection of genetics and chemical modifiers of certain phenotypes, time and cost. Due to the entanglement of the neuronal network, monitoring of *in vivo* subcellular processes in vertebrate's models is a tedious work. Furthermore, an accomplishment of constant experimental conditions for intrinsic and extrinsic factors is a challenging task. To shroud these limitations, nowadays researchers focal point is the utilization of invertebrate models which are convenient in terms of time frame, cost, progeny, disease-associated transgenic lines expression, high-throughput screening capability to identify disease-related specific genes and molecular pathways [14,16,18]. The availability of potent experimental tools in invertebrates, enabled researchers to some extent, to understand the basic biology and etiology of neurodegenerative diseases [18] (Table 2). Currently, various kinds of invertebrate models are under researcher's utilization for the discovery of the potent and novel therapies for PD. In this paper, we review some of the prominent invertebrate models on PD research.

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Table 1: Parkinson's disease manifestations possible treatment.

Signs/symptoms	Primary treatment	Surgical treatment	References
Parkinsonism	Levodopa, Dopamine Agonists	GPI DBS, STN	[145]
Dyskinesia	Amantadine	GPI DBS, STN	[146,147]
Motor Fluctuations	MAOI, COMTI, Levodopa ER	STN, GPI DBS	[148]
Dystonia	Botulinum Toxin	STN, GPI DBS	[149,150]
Rest or Re-Emergent Tremor	Levodopa, Botulinum Toxin, Anticholinergics	GPI DBS, STN	[151]
Behavioral Problems, Psychosis, Hallucinations	Quetiapine, Clozapine, Pimavanserin		[152]
Depression, Anxiety	SSRI, SNRI, Tricyclics, Benzodiazepines, Pramipexole		[153]
Dementia	Rivastigmine, Donepezil, Galantamine, Memantine		[154]
Apathy	Methylphenidate, Levodopa, Selegiline		[151]
Orthostatic Hypotension	Midodrine, Fludocortisone, Droxidopa		[154]
Bladder Dysfunction	Anticholinergics, Pelvic Floor Exercise		[155]
RDB	Clonazepam, Melatonin, Quetiapine		Sophie E Legge
EDS	Modafinil		[151]
Insomnia	Trazadone, TCAs, Zolpidem, Melatonin, Eszoplicona		[156]
Pain	NSAIDs, BoNT, Opiates, Antidepressant		[153]

COMTI: Catechol-O-Methyl Transferase Inhibitor; ER: Extended Release; GPI: Globus Pallidus Interna; MAOI: Monoamine Oxidase Inhibitor; SNRI: Serotonin Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; STN: Sub Thalamic Nucleus; DA: Dopamine Agonist; DBS: Deep Brain Stimulation; TCAs: Tricyclic Antidepressant; RBD: REM Sleep Behavior Disorder; EDS: Excessive Daytime Sleepiness; BoNT: Botulinum Toxin; NSAIDs: Non-Steroidal Anti-Inflammatory Drug.

Table 2: Caenorhabditis elegans genes are orthologous of human genes related to neurodegenerative disorders.

Human genes	*C. elegans*	References
Huntingtin (Htt)	n/a	[157,158]
Amyloid Precursor Protein (APP)	apl-1	[159]
β-secretase (BACE1)	n/a	[160]
Presenilin-1 and 2 (PS1 and PS2)	sel-12, hop-1, spe-4	[161]
Microtubule-Associated Protein Tau (MAPT)	ptl-1	[162]
PARK1	n/a	[163]
PARK2	pdr-1	Artal-Sanz and Tavernarakis
PARK5	ubh-1	Wolinsky
PARK6	pink-1	[164]
PARK7	djr-1.1 & djr-1.2	[157]
PARK8	lrk-1	[113]
PARK9	catp-6	[160]
PARK11	n/a	[113]
PARK13	n/a	Artal-Sanz and Tavernarakis
SMN1/SMN2	smn-1	[76]
SOD1	sod-1	Van Raamsdonk and Hekimi

n/a: Not Applicable.

The Invertebrate Animal Models on PD Research

Planaria

Dugesia japonica freshwater planarians belong to phylum *Platyhelminthes*, which secured a Central Nervous System (CNS), composed of brain and pair of ventral nerve cords. *Planaria* are simplest animals similar to vertebrates and most invertebrates with distinguishing features of bilateral symmetry, dorsal and ventral surfaces what is more have a rostro caudal axis with a head and a tail. The head possesses optical, chemical and vibratory sensors. Functionally and anatomically, *Planaria* brain is well organized as they contain neural populations of different neurotransmitters like Dopamine (DA), serotonin, Gamma-Aminobutyric Acid (GABA), Octopamine, acetylcholine, and neuropeptides. Their CNS have cholinergic and dopaminergic neurons analogous to human [19-21]. One of the distinctive characteristics of *Planaria* is that they can regenerate the lost tissues including that of the nervous system *via* their pluripotent stem cells called 'neoblast 'and this regeneration is facilitated by a specific gene named nou-darake. *Planaria* has well established

dopaminergic system and having a neuronal marker gene named *D. japonica* Tyrosine Hydroxylase (DjTH) [22-24]. The locomotary defect is one of the signs of PD and it is concerned with the loss of dopaminergic neurons [25]. *Planaria* responds with characteristic screw-like hyperkinesia and C-like position behavioral changes upon exposure to drugs acting on acetylcholine or dopamine systems. This distinguishing feature of *Planaria* can be used for the screening of therapeutic potential of both natural and synthetic compounds on PD. The opioid system has a role in locomotary activities, and certain research studies have proven that stimulation of k-opioid receptors in *Planaria* indirectly enhances dopamine transmission. *Planaria* has a well-developed dopaminergic neuronal system and they respond to neuronal reuptake inhibitors, dopaminergic agonists and antagonists with characteristics changes in locomotion and behavior [26-28]. *Planaria* has been traditionally used in toxicological research [29]. Neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, rotenone, and 6-hydroxydopamine (6-OHDA) are the main sources of Reactive Oxygen Species (ROS) production in an abundant amount that causes dopaminergic neuronal loss and produces Parkinsonian phenotypes [30]. *Planaria* provides a novel parkinsonian model for the investigation of drugs acting as protective agents against neurotoxin mediating dopaminergic neuronal loss in neurodegenerative diseases, especially in PD [31,32]. Metals especially trace metals dyshomeostasis plays a significant role in the PD pathogenesis [33,34]. Utilization of *Planaria* as a model can help us in a sophisticated way to investigate metals dyshomeostasis in the form of producing 3-dimensional screw-like movements and this phenomenon is comparable to that of stereotyped behavior produced in mammalian [35,36].

Tyrosine Hydroxylase (TH) the first and rate-limiting step-catalyzing enzyme in the biosynthesis of catecholamine and its deficiency is a hallmark of PD. The deficiency of the TH results in behavioral changes such as movement speed and direction. *Planaria* characteristic anti-tropism (light avoidance behavior upon exposure to light) phenomena associated with neurotransmitter system could be used as a novel behavioral test to screen out neuroprotective therapeutic compounds [23]. The Djsnap-25 and DjGAD genes in *Planaria* are responsible for this anti-tropism behavior [22]. *Planaria* due to simplicity in the organization, rapid progeny, low cost, high throughput and response to a variety of drugs acting not only on the dopaminergic and cholinergic nervous systems but also on other pathways related to other neurotransmitters serves as a convenient model for PD research. *Planaria* models are successfully used for the investigation of different drugs effect like that of DMSO toxicity [29], behavioral sensitization of cocaine [37], agents acting on monoaminergic systems like Reserpine, haloperidol, apomorphine hydrochloride [38], 3-Iodo-L-tyrosine and dopaminergic agonists talipexole [31]. These *Planaria* models veil the behavioral difficulties related to other animals models [39]. Due to the distinguishing characteristic of regeneration, this model can be used to investigate the neuro-regenerative medicine to treat neuro-degenerative diseases such as PD [22].

Tribolium castaneum (red flour beetle)

The *Tribolium castaneum* (*T. castaneum*) with the entirely sequenced genome is an emerging candidate for the investigation of various diseases pathogenic studies. The focal point of the biomedical researchers is on the untangling mechanistic of the basic life processes such as feeding, neurotransmission, the activity of immune system as well as mechanistic clarification of different diseases such neurodegenerative, cardiovascular and metabolic diseases. Due to convenience in terms of ethical concerns, progeny, cost, time frame, fully sequenced genomic system and ease of oral administration of test compounds enables the *T. castaneum* to be utilized as an investigative tool in the field of life science research [40,41]. Depletion in the corpus striatum Dopamine levels of PD patients leads to certain behavioral changes [42]. *T. castaneum* shows a characteristic behavioral phenomenon known as tonic immobility, and its occurrence is concerned with the brain dopamine levels depletion. *T. castaneum* can be used as an investigative tool for screening therapeutic potentials of the new drug candidates in neurodegenerative diseases by observation of tonic immobility after compound ingestion [40,43]. Ageing is a progressive deterioration in the functional and structural well-being of the body. Ageing causes the disturbance of normal metabolic and social fitness. Ageing is a major risk factor for the most prevalent neurodegenerative diseases, including Huntington's Disease (HD), PD and AD. Ageing disturbs the homeostasis between ROS production and antioxidant due to which oxidative stress is produced and it causes the damage of various biomolecules. For slowing down age-associated cellular damage and their consequences, scientists have discovered various pharmacological interventions such as insulin signaling pathway, epigenetic pathway, mTOR pathway and dietary restriction. Currently, researchers are focusing on the use of plant-based drugs due to their high antioxidant capacity for the treatment of various acute and chronic diseases including neurodegenerative diseases [44]. To screen various plant-based drugs efficiency and their ameliorating effect on disease pathogenesis an accessible model is required and in this case, *T. Castaneum* is most suitable due to its characteristic of food consumption through the mouth. *T. Castaneum* has been successfully used as a screening platform for gene-food interactions. *T. Castaneum* genome having longevity and stress tolerance sirtuin genes (sirt-1 and sirt-3 based on their closest relatives in other species). Due to these distinguishing characteristics, RNA interference (RNAi) can be used to investigate the relevance of different genes and signaling pathways in stress resistance and ageing. Thus, this *T. castaneum* is most promising in screening the most vital active compound of the plants and whose effect can be investigated in most complex models in future [45]. Phosphatase and Tensin homolog (PTEN-) induced kinase 1 (PINK1) gene is acting as a sensor for mitochondrial damage and clear the damaged organelles by Parkin activation and is required for mitochondrial quality control. PINK1 phosphorylates Ser65 in both ubiquitin and the Ubiquitin-like (Ubl) domain of Parkin, which stimulates its E3 ligase activity. Auto phosphorylation of PINK1 is required for Parkin activation. Mutations in PINK1 cause autosomal recessive PD. To investigate the intrinsic catalytic properties of PINK1 and molecular mechanisms for the recognition and phosphorylation of Ub and Ubl required for Parkin activation different models with mammalian PINK1 orthologues have been using by researchers, and among them, *T. Castaneum* PINK1 (TcPINK1) is the most active orthologue [46]. By utilization of *T. Castaneum* TcPINK enabled researchers to successfully investigate that substrate specificity of PINK1, the effect of PD-associated PINK1 missense mutations and the crucial importance of the PINK1 kinase activity in PD prevention.

Table 3: The role of *C. elegans*, *Planaria*, *T. Castaneum*, *D. melanogaster* in understanding the mechanism of PD pathogenesis and novel drug discovery.

Name of Invertebrates Models	Role in PD Untangling Mechanistic and Novel Drug Discovery	References
	Utilization of available experimental tools in these models enabled researchers to understand the basic biology of PD and screening of different potent compounds	
Planaria	DA Agonist	[35]
	Drug of Abuse	[37]
	TH Inhibitors	[165]
	Regenerative Drugs	[22]
	CNS Acting Drugs	[166]
	Neurotoxic Drug	[31]
Tribolium Castaneum	Screening of Potential Therapeutic Compounds	[42,43]
	Genetic Mutations	[47,48]
Drosophila melanogaster	Genetic Mutations	[56]
	Screening of potential therapeutic compounds	[167]
	Genotypic-phenotypic relationships	[46]
	Non-motor dysfunction	[51]
	Genetic-environmental interactions	[168]
	Different Biochemical Pathways and their Impact on PD	[50,169]
	Neurotoxic Substances	[60]
	Behavioral Dysfunction	[53]
Caenorhabditis elegans	Genetic Mutations	[10,17,110]
	Screening Potent Therapeutic Compounds	[130,131]
	Screening of Cholesterol Metabolism impact through Nceh-1 gene	[170]
	Autophagy Dysfunction through LGG-1 gene	[171]
	Molecular Chaperon i-e Hsp-70 role in PD	[172]
	Neurotoxic Substances and their Impact on Disease Pathogenesis	[173]
	DA Receptors Effect on Behavior	[101]
	The Detrimental Effect of Metals	[116]
	Impact of Different Molecular Pathways	[137]

DA: Dopamine; TH: Thyroxine Hydroxylase.

By using insects like *T. castaneum* enabled the researchers for the first time to develop assays for quantitative assessment of PINK1 activity and its substrate specificity These findings will be helpful in future for PINK1 substrates investigation and its role in PD [47,48].

Drosophila melanogaster

Drosophila melanogaster (*D. melanogaster*) "fruit fly" is one of the most extensively used models in the scientific research of neurodegenerative diseases. Due to ease of culture, low cost, rapid progeny, well-developed anatomy, genomic sequencing, characteristics of gene inactivation by RNA interference, well organized dopaminergic system, the relatively short life cycle (approximately 10 days) and lifespan of flies (2 to 3 months) accelerate the study of age-related disorders including PD. The neurons are divided mainly into two groups, the major protocerebral anterior medial group (100 neurons) and minor Protocerebral Anterior Lateral (PAL).

PAL consists of protocerebral posterior medial, the protocerebral posterior lateral, the Thoracic 1, and the ventral unpaired median group each of these contains a group of 5-10 neurons. These different groups involved in the control of locomotion and other complex behaviors including olfaction, memory, learning, courtship, reward and sleep. *D. melanogaster* are amenable for large-scale genetic and chemical screening, thus providing opportunities for not only understanding the genetic and molecular basis of diseases but also for novel drug discovery.

D. melanogaster has approximately 300,000 neurons having organizational and functional specificity and similarity with mammals, lack of blood-brain barrier, which help in the assessment of therapeutic compound without the additional concerns of brain uptake [49-51]. To study the cellular and molecular basis of disease forward genetic approach has provided tremendous results. One of the distinguishing features of *D. melanogaster* is that of having specific eye retina tissues for direct expressional studies. *D. melanogaster* retina is composed of approximately 800 identical eye units termed as "ommatidia" and it can express the degenerative changes in cellular patterns and act as an investigative tool in genetic research [50,52,53].

Epidemiological studies have proven the contribution of genetic mutations in Familial PD (FPD). To date, six FPD genes have been molecularly cloned, including SNCA, Parkin, Ubiquitin C-terminal hydrolase-1 (Uchl-1), DJ-1, phosphatase and Tensin homologues

(PTEN)-inducedkinase1 (PINK1), and leucine-rich repeat kinase 2 (LRRK2). *D. melanogaster* has 50% genetic homology in entire genetic pathways with human and 60-70% of human disease genes possess drosophila counterparts. Due to these characteristics, *D. melanogaster* provides a sophisticated model to investigate the effect of the mutation on the behavioral phenomenon, dopamine level changes and basic molecular mechanism of the disease pathogenesis. A Mutations at three loci of the SNCA, Uchl-1 and Parkin members cause defective degeneration of the misfolded protein in disease mechanisms [54]. Though the *D. melanogaster* genome does not encode an SNCA homolog, pan-neuronal expression of either wild type or mutant SNCA (A53T and A30P) provide a basic insight into several features of PD. The chaperone family Hsp70 and Hsp40 plays a vital role under stress conditions in the proper folding of the proteins. Simultaneous overexpression of human Hsp70 with α-synuclein in *D. melanogaster* leads to remarkably efficient suppression of dopaminergic neuronal death and this effect is investigated by feeding *D. melanogaster* with geldanamycin, which increases the endogenous level of Hsp70. Thus the large scale genetic screening capability of the *D. melanogaster* model is providing promising therapeutic strategies for human neurodegenerative disorders [49,52,55]. Advanced pharmacological research indicates that the active compounds of plants provide protective effects against neurotoxicity in models of PD. Researchers are utilizing Pharmacological models for screening therapeutic potential of different chemicals, in this scenario, *D. melanogaster* characteristic of direct feeding can be avail for screening therapeutic effect of different chemicals by the direct observation of its different behavioral changes [51,56-59]. Epidemiological studies have suggested that environmental toxins including pesticides, herbicides, fungicides exposure are one of the risk factors of PD. A meta-analysis study reported a 62% increase in PD risk due to exposure to pesticides. Similarly, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its analogue paraquat, one of the most widely used herbicides exposure causes rapid, non-progressive DA neuron loss and associated motor disabilities in humans. *D. melanogaster* can be utilized to investigate the direct effect of these toxins by observation of declination in the climbing ability which is directly associated with a decrease in DA signaling due to increased dopaminergic neurodegeneration in the brain. Later these results can be translated in higher animal's models for the investigation of further molecular mechanisms of the disease pathogenesis [51,60,61]. Over 90% of patients developed abnormality in sleep rhythm during PD due to DA levels alteration in the brain. *D. melanogaster* can be employed to study circadian changes. The *D. melanogaster* circadian cycle control several behavioral and physiological processes especially locomotary activity. Several studies suggesting that the increase in circadian cycle abnormality is mainly due to SNCA aggregation. By availing, the opportunities of ease in advanced genetics techniques implementation and downregulation or overexpression of specific genes in *D. melanogaster*, circadian cycle abnormality can easily be examined. Later these results can easily be intervened that whether or not circadian rhythm abnormality is involved in the enhancement of neurodegeneration and presenting an additional risk factor for PD pathogenesis [53,62,63]. The B type Cell Lymphoma 2 (BCL-2) family of genes composed of pro-apoptotic and anti-apoptotic members play a pivotal role against apoptosis in animals. Drosophila due to having distinguished characteristics of age-associated loss of dopaminergic neuron, reduction in locomotor function, besides, of having BCL-2 family members' homologues that are anti-apoptotic Buffy and pro-apoptotic Debcl presented a widely successful and applied model to investigate the role of BCL2 family member's proteins in disease progression. Similarly, Drosophila due to possession of Transmembrane Bax Inhibitor-1 Motif-containing (TMBIM) family homologues and the ability to display some features of PD like loss of dopaminergic neuron and locomotary function with age helps in sort out the role of Bax Inhibitor-1 (BI-1) in neuroprotection against apoptosis [64-66]. The pathogenic role of mitochondrial dysfunction and altered expression of high-temperature requirement A2 (HtrA2; also known as Omi) in neurodegeneration has been highlighted through the use of *D. melanogaster* model of PD and helped in the investigation of the role of various PD-linked genes in disease pathology [67]. Oxidative stress one of the important factors in PD progression is linked with the presence of LB in the diseased patient brain. Natural products due to having the potential of scavenging free radicals and influence on the pathogenesis of neurodegenerative diseases are recently one of the main focus of researchers for searching therapies for debilitating diseases. The transgenic *D. melanogaster* models due to the expression of wild or mutant types of human alpha-synuclein under GAL4/UAS system are providing the best opportunities to screen plant-based products potentials as antioxidant therapies for neurodegenerative diseases [68-70]. In short, *D. melanogaster* has contributed substantially in in sighting PD mechanism due to having ease of study behavioral defects, histology, physiology and different PD-concerned genetic interactions.

Caenorhabditis elegans

Caenorhabditis elegans (*C. elegans*) was first used in the 1970's as a model animal for investigation of neurodegenerative diseases [71]. *C. elegans* due to highly conserved genomic sequencing with approximately 83% human genes orthologous and at least 42% of human disease-related genes orthologous and metabolic pathways with the mammalian system is presenting itself as a powerful genetic tool. Besides, *C. elegans* have orthologous of genes related with polyglutamine repeat diseases [72], AD [73], PD [74], Amyotrophic lateral sclerosis [75], Spinal Muscular Atrophy [76] (Table 2). Due to advantages of small size, ease of laboratory maintenance, short life span, low-cost, fast reproduction, ease of reporter gene fusions, ease of genome manipulation, ease of handling, high throughput screening and transparent body makes this model one of the best models [77-79]. The prime advantages of *C. elegans* is its well-developed nervous system, which is structurally and functionally similar to mammals. The nervous system composed of 302 neurons having eight dopaminergic neurons, subdivided into three main groups cephalic, anterior deirid and posterior deirid neurons with 5 dopamine receptors among which two are homologous to mammalian D1-type receptors (dop-1, dop-4) and three are homologues to D2-type (dop-2, dop-3 and dop-6) with a dopamine transporter the dat-1 [4,80,81]. Another striking feature of the *C. elegans* is the reverse genetics that is knockdown target genes by simply injecting, soaking, or feeding worms dsRNA, which is complementary to the targeted and subsequently silenced gene [82]. By the introduction of this method, Andrew Fire and Craig Mello later received the 2006 Nobel Prize in Physiology [83]. Epigenetics plays a vital role in PD pathogenesis; epigenetic marks are known to be inherited from generation to

generation. The *C. elegans* due to the short life span providing an opportunity as an ideal model to determine the effect of a specific environmental factor or drug exposure that lasts for multiple generations after exposure has ceased, and thus led the way in the discovery of novel genes that influence chromatin landscapes in the ways that influence PD phenotypes [84]. SNCA was first discovered in 1985 [85,86]. Polymeropoulos and colleagues in 1997 discovered that a single point mutation in SNCA Ala53Thr leads to an inherited form of PD and a family having this genotype have 85% chances to get the disease [87,88]. Currently the main challenge is the discovery of the most potent drug, which can cure the root cause of the disease. A number of plant-based drugs have been found with neuroprotection action. For the proper screening of these candidate compounds therapeutic values a model, system with convenient *in vivo* assays is always required. As mammalian disease models are expensive and time-consuming, therefore a rapid and inexpensive model system is the main priority of researchers. Here the *C. elegans* can be utilized for screening therapeutic values of different compounds [89]. *C. elegans* do not have the SNCA homolog; therefore, it presents the opportunity to investigate the interaction of SNCA with other genetic defects and its pathological role in PD [10]. Transgenic *C. elegans* with overexpression of human SNCA in various cell types i-e in pan-neuronal, dopaminergic neurons and body muscle walls provide the opportunity of cellular pathology of various synucleopathies to some extent [90-92]. Transgenic *C. elegans* can be used to investigate the therapeutic potentials as well as to get insight into the mechanisms of various phytochemicals [93-95]. Dopamine plays a crucial role in several physiological processes like endocrine function, memory, emotion and cognition and their dysfunction and degeneration have shown severe neurobehavioral disorders [30,96]. Despite decades of investigations, the mystery of dopamine role in neurological diseases is still unclear. To investigate the role of dopamine in neurodegenerative diseases and its molecular pathways is one of the main focuses of research. The complexity of the human brain which contains over 100 billion neurons and tens of thousands of DA-containing cells, relative inaccessibility of vertebrate's dopaminergic neurons, besides, the inability of *in vivo* direct visualization of dopaminergic neurons restricts the progress in the clarification of molecular pathways involved in the dopaminergic neurodegeneration. In this regards the *C. elegans* having distinguishing characteristics of body transparency enable *in vivo* visualization of cell morphology and protein expression patterns. This feature can be used to get insight into PD pathology. *C. elegans* have well developed dopaminergic system and it was first identified in 1974 by J. Sulston and colleagues [78,97,98]. PD is a movement disorder [99]. *C. elegans* have specific behavioral and locomotary action related to the dopamine [100]. This behavioral plasticity of the *C. elegans* can be used to investigate the therapeutic potential of natural compounds in ameliorating the toxicity of dopamine in neurodegenerative diseases [101,102]. Genetic factors contribute to the pathogenesis of PD up to 10%. The eminent genes contributing to PD risk factors are α-synuclein, leucine-rich repeat kinase 2 (LRRK2), glucocerebrosidase, DJ-1, PINK-1, and Parkin [103,104]. Parkin gene mutations contributed up to 50% for autosomal recessive, early-onset, familial form of PD [105]. LRRK2 encoding gene point mutation account for about 3% of the overall causes of autosomal dominant PD [106]. DJ-1 plays an important role in the protection of neurons from oxidative stress and its mutation is concerned with the Autosomal Recessive Early-Onset Parkinsonism [17,107]. To study the pathogenic role of genetic mutations in Parkinsonism *C. elegans* due to having homology with mammalian genes provide the best model. *C. elegans* have the orthologs of LRRK1 and 2 in the form of lrk-1 and its deletion or knockout can give an important insight into different behavioral phenotypes related to PD [71,108]. *C. elegans* has a homologue of the PTEN-induced kinase pink-1 gene and LRRK2 and by the utility of this characteristic, scientist for the first time came to know that these PINK-1 and LRK-1 genes having an antagonistic role [109,110]. Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) and Cerebral Dopamine Neurotrophic Factor (CDNF) are the members of a novel family of Neurotrophic factors (NTFS) of invertebrates, and they play a key role in dopaminergic neurons protection. To investigate the molecular mechanism of MANF gene *C. elegans* due to having MANF gene homolog manf-1, provide the opportunity as a model. By availing this opportunity in *C. elegans* scientists proved that manf-1 mutant has an effect on the age-dependent declination in dopaminergic neurons survival. In addition, they show failure in the regulation of ER unfolded protein response (ER-UPR) [111-113]. MANF neuroprotective and neurorestorative function has been confirmed by researchers by using specific neurotoxin model of *C. elegans* [114]. Epidemiological studies suggest that increased prevalence of PD in rural areas is associated with the use of pesticides, herbicides, and heavy metals [115]. The postmortem studies of the neurodegenerative disease deceased brain tissues revealed the most compelling evidence of the metal accumulation relationship with neurodegenerative diseases [116]. Excessive brain iron accumulation causes a Neurodegeneration with brain iron accumulation syndrome previously known as (Hallervorden-Spatz syndrome) consists of a group of rare autosomal recessively transmitted neurodegenerative disorders with progressive symptoms of an extrapyramidal dysfunction including dystonia, rigidity, and choreoathetosis. Several postmortem studies revealed that the iron accumulation in Parkinsonian SNpc region is increased up to 35% [117]. An elevated level of iron interacts with SNCA [118]. Mitochondrial dysfunction is also related to elevated iron level [119]. Excessive manganese exposure causes a toxic condition known as "manganism" identified by James Couper in 1837, causes the irreversible damage of the same region of basal ganglia implicated in PD [120,121]. *C. elegans* offering a powerful *in vivo* model system for studying neurodegenerative disease and gene-environment interactions. *C. elegans* behaviors related to DAergic signaling including basal slowing response, area-restricted searching, and tap withdrawal response can be used to study different metal neurotoxicity. By using this model researcher have got insight to some extent into the role of metal transporters and metal homeostasis in the etiology of neurodegenerative disease. This model can be further used in future to screen different metals and xenobiotic suspected of inducing neurodegeneration [116,120,122]. Manganese causes an extrapyramidal syndrome that resembles PD. The symptoms include rigidity, tremor, gait disturbances and hypokinesia. Mutations in the SLC30A10 gene have been reported to induce a genetic manganese overload syndrome and causes moment disorder [123,124]. *C. elegans* is a powerful model due to its well-developed nervous and genetic system. DJ-1 gene act as a cytoprotective antioxidant protein in verity of the toxic condition and proved from several studies that this gene protects the *C. elegans* from

manganese induced DAergic toxicity in an age-dependent manner [125]. Divalent Metal Transporter 1 (DMT1) is the primary manganese importer, besides; it also transports a variety of divalent metals including iron. To investigate the role of this transporter in PD pathology *C. elegans* provide the best opportunity due to having DMT1 orthologues SMF-1, SMF-2 and SMF-3. And utilization of this model has successfully proved that due to manganese (Mn) sharing transporters with iron (Fe) and as a consequence of transportation competition Fe level become reduced with the elevation of Mn level [126,127]. To date, existing PD therapies provide symptomatic [128]. Plant-derived components or phytomedicines such as alkaloids and flavonoids have been used from the ancient times against Neurodegenerative Disease (NDDS). Phytochemicals from medicinal plants can provide a better and safer alternative to synthetic molecules [129]. *C. elegans* can be utilize to screen out the neuroprotective effect of different phytochemical [89,99]. Several antioxidant and anti-ageing phytochemicals compounds have been successfully screened by using this model [44,130,131]. Oxidative stress and mitochondrial dysfunction are one of the main causes of PD etiology. By the utilization of the *C. elegans,* numerous plant-based compounds antioxidant and mitochondrial function ameliorative effect have been screened out [132-134]. The mammalian Nrf (NF-E2-related factor) (Nrf1, Nrf2, Nrf3, p45 NF-E2) protein is antioxidant and xenobiotic defense regulator; in addition, they perform a role in cellular protection and maintenance. For the exploration of mechanisms that how the Nrf/CNC proteins play a role in antioxidant regulation *C. elegans* provide the opportunity because of having Nrf/CNC proteins sequence and functional orthologs SKN-1 [135,136]. By using a *C. elegans* model researchers have proved that how NRF-2 pathways are regulated beside the dopaminergic neurons protection against metals and other neurotoxins toxification [137,138]. Striking evidence revealed that in PD biogenic amine system destruction occurs. A versatile model system of *C. elegans* has been used to study the molecular mechanism of biogenic amine system destruction suggesting that the p38 MAP kinase pathway plays a crucial role in *C. elegans* innate immunity against biogenic amine system destruction toxicity and may play the same role in higher organisms [139,140].

Limitations of Invertebrate Models

Despite all the outstanding advantages of invertebrates, there are several disadvantages. In vertebrates, the brain regions and circuitries studied have obviously relevant and homologous human counterparts, where in invertebrates; the homology is not obvious [141]. In mammals, all animals belong to same class and body plan and brain structures are largely conserved, wherein invertebrates belong to different phyla, body plan and range of nervous systems. The morphological homology of brain regions between vertebrates and invertebrates is not obvious [142]. The neurocircuitry and specific anatomy of vertebrates and invertebrates are totally different [143]. Mostly have simple body plan, and lack of defined organs/tissues including brain, blood, fat cells, internal organs. Their bodies are small which make biochemistry very difficult. Generally, microarray, immunoprecipitation, and chromatin immunoprecipitation is conducted in mixture of whole animal's extract of either mixed-stage or similar growth stage. This create confusion in understanding of any specific tissue signaling [144]. It would be very difficult to argue that any results on neuro-anatomical level would directly translate from invertebrates to vertebrates.

Conclusions

Pharmacological therapies for PD has so far had some achievement in terms of symptomatic relief. On the other hand, extensive research is needed to establish a precise and fundamental disease-modifying therapeutic approach in PD. For the discovery of potential therapies and mechanistic insight into the disease pathogenesis, different researchers have used numerous disease models. The human and higher mammalian models have limitations due to ethical concerns, cost and lengthy time frame. Invertebrates are the suitable alternatives to higher mammalian models in the above limitations. Different invertebrate's models have been in use and although not all recapitulated the perfect pathogenesis of PD, each to some extent has provided opportunities to insight into certain aspects of the disease. The basic logic of using these invertebrate models is that they enabled researchers to apply the potent experimental tools available in these organisms to understand the basic biology of neurodegenerative diseases. The use of the forward genetic screening approach of the invertebrates has shown tremendous results in the identification of novel genetic factors that modify the risk of PD. These models helped in disclosure of new molecular pathways as potential therapeutic targets that are directly translatable into higher-order systems and can be used in future in the development of an efficient treatment strategy for this complex disorder. It is anticipated that ongoing and future genetic modifier screens in these invertebrate models will generate further mechanistic insights into the disease processes. The basic knowledge gained through these models can be translated into higher animal's model to get a more precise insight into the biochemical and molecular pathways. Based on current knowledge gained by the utilization of these invertebrates models in terms of the etiology, pathogenesis, and mechanism of PD, numerous neuroprotective strategies might be devised. Several research goals can be devised from the discovery of multiple PD-related genes and phytochemicals potential therapeutics. Scientists must search for the creation of etiologic specific PD animal models for the identification of links between the molecular pathways modified by diseased -associated genes. The investigation of these aspects will enable scientists shortly that what makes the dopaminergic neurons susceptible to degeneration in PD as well to test and devise the novel therapies for this devastating disease.

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