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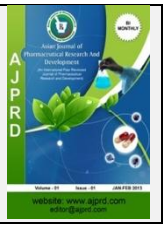

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Review Article

An Overview of Animal Models and Symptomatic Treatment of Parkinson's disease

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A B S T R A C T

The broad theory indicate that neurological ailment is caused by intricate interactions between environmental and genetic factors is supported using animal models to better understand the the cause and pathogenesis of Parkinson's disease (PD), as well as its cellular and molecular mechanisms. The more recent models use genetic manipulations that either introduce mutations similar to those found in familial cases of PD (a-synuclein, DJ-1, PINK1, Parkin, etc.) or selectively disrupt nigrostriatal neurons (MitoPark, Pitx3, Nurr1, etc.). "Classic" models are based on neurotoxins that specifically target catecholaminergic neurons. All of these together each model has its own benefits and drawbacks. The use of medication, deep brain stimulation, and physical therapy has been optimised for the symptomatic treatment of the motor symptoms of Parkinson disease (PD). L-dopa, several dopamine agonists, inhibitors of MAO-B and catechol-o-methyltransferase (COMT), and amantadine are among the pharmacotherapies available.

Keywords: -Parkinson disease, Models, Toxicant, Genetic, Treatment.

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INTRODUCTION

Parkinson was first described by James Parkinson. (PD) in 1817. It is a chronically progressive neurodegenerative illness that affects at least 1 % of people over 55years.[1] Around the world, there are 10 million people with PD, and it affects 2 -3% of those over 65. More people are becoming disabled and dying due to Parkinson's disease (PD) globally than any other neurological condition. In the last 25 years, PD prevalence has doubled. Parkinson's disease affects men 1.5 times more frequently than it does women. The majority of Parkinson disease diagnoses are made in patients 65 years of age [2]. Until the early 20th century, when the German pathologist Frederick Lewy observed neuronal cytoplasmic inclusions in several brain locations, the pathology of PD was not well known. The loss of neurons in the substantia nigra pars compacta (SNc) of the midbrain, according to Tretiakoff's observations in 1919, is the most significant anomaly in Parkinson's disease (PD). Dopamine's significance and its depletion from the basal ganglia were found by researchers in the 1950s as the key to understanding the pathophysiology and pathologic biochemistry of Parkinson's disease.[3]

Among the key neurochemical characteristics Dopaminergic nigrostriatal pathway degeneration causes parkinsonian diseases.[4] Animal models are utilised for anything from basic research testing of novel treatments or vaccine resulting in closely watched advances in medical knowledge.[5] Parkinson's disease's clinical symptoms include problems with motor coordination such as muscle rigidity, tremor, postural instability, hypersalivation, bradykinesia, and slowness of movement (PD). Mood disorders, sleep issues, cognitive impairments, pain, anxiety, and depression are examples of non-motor symptoms. A Parkinson's illness Age, catalepsy, brain damage, exposure to chemicals, environmental and genetic influences, severe psychiatric problems are some risk factors.[6]

Models used in Parkinson disease: -

Three categories can be used to group animal models of Parkinson's disease: those based on neurotoxins or neuropharmacological substances that target catecholaminergic neurons; those based on genetic alterations related to the disease. This is primarily because each model is based on the production of one or a small number of PD pathological processes, which are either artificially induced in a way that is rarely relevant to the disease (such as toxin models) or that is relevant to the disease but only produces a small portion of the pathology (such as genetic models).[7,8]

Neurotoxin models: - Animal models for PD have been created using a variety of poisons and pharmaceuticals. Typically, neurotoxins are known to cause severe nigrostriatal degeneration. significant motor symptoms (however, notably in rodents, these symptoms are rarely equivalent to those found in PD patients). As a result, these models are ideal for researching the neurodegenerative processes that affect SNc DAergic neurons and testing symptomatic medications. [9,10]

6-OHDA: - A structural analogue of catecholamines is 6-OHDA. The traditional animal model of PD is 6-hydroxydopamine (6-OHDA) Since the late 1960s, PD has been studied using 6-OHDA, a structural homolog of catecholamines, primarily in rodents. [11,12] 6-OHDA causes the nigrostriatal system to slowly retrograde over the course of a week. This molecule, being hydrophilic, is unable to penetrate the blood-brain barrier (BBB), hence it must be stereotaxically injected directly into the target brain structure, which is typically the striatum, MFB (medial forebrain bundle), or SNc. It has also occasionally been administered intracerebrally. 6-OHDA's neurotoxicity is caused by a two-step mechanism that involves the The DA accumulates the chemical into catecholaminergic neurons. and noradrenaline membrane transporters and its inhibition of mitochondrial complex I [13].6-OHDA creates an intracellular oxidative stress by using the DA transporter to enter the cytosol, where it can auto-oxidize. After 2-3 days of striatal dopamine depletion, 6-OHDA infusion into substantia nigra or nigrostriatal tract dopaminergic neurons causes their degeneration within 24 hours. In the brain's striatum, 6-OHDA has a negative impact on GSH and SOD activity and an increase in malondialdehyde levels. [14,15] Because it is thought and proven that the TH-positive terminals in the striatum die before the TH-positive neurons in the SNpc, which is thought to be a replication of the PD picture, many researchers have directly injected this substance into the striatum to study retrograde degeneration [16]. 6-OHDA creates an intracellular oxidative stress by using the DA transporter to enter the cytosol, where it can auto-oxidize.[17]

MPTP:- MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was first identified as having neurotoxic properties in the early 1980s when drug-dependent Californians accidentally injected "synthetic heroin" contaminated with MPTP (1-methyl-4-phenyl-4-propionoxypiperidine, also known as MPPP or dimethylpyridine.[18] These individuals suddenly experienced parkinsonian symptoms. . Once MPTP in the brain is taken up by the astrocytes, and is metabolized to MPP+, its active metabolite, by monoamine oxidase-B (MAO-B). Recent findings show that once released from the astrocytes enters the extracellular environment via the OCT-3 transporter [19], MPP+ is taken up into the neuron by the dopamine transporter and can be stored in vesicles via uptake by the monoamine transporter vesicular In order to create experimental PD models, MPTP, a highly lipophilic that readily crosses the BBB, can be administered systemically. MPTP is often taken systemically (subcutaneous, intraperitoneal, intramuscular, intravenous). Acute MPTP exposure causes the substantia nigra pars compacta to lose 50% to 93% of its cells and the striatum to lose more than 99% of its dopamine. This causes a particular degeneration of the nigrostriatal dopaminergic pathway.[20] Typically, MPTP-treated mice experience motor dysfunction that can be identified by behavioural tests that are alert to even the slightest [21]variations in DA levels. Several low dose injections are typically used in protocols for monkeys. These injections typically result in persistent loss of DAergic neurons, as well as akinesia, "freezing," bradykinesia, muscle rigidity, aberrant posture, stereotypy, and occasionally tremo.[22] Application of MPTP having Pharmacological and genetic therapies intended to protect dopamine cell are being tested in preclinical studies to help with symptoms. The MPTP model of Parkinson's disease has some drawbacks, such as being often acute, non-progressive, and reversible, with inclusion bodies being uncommon.[23]

Paraquate and Maneb: - cybersquat for potential application as a pesticide in the 1950s. Paraquat (N,N-dimethy l4-4-4 \s-bipyridinium) is used frequently in agriculture. An herbicide, that is. According to epidemiological studies, using pesticides raises The risk of finding Parkinson's disease.[24] based on the active metabolite of MPTP, MPP+, and its structural similarities. Albeit slowly and to a small extent, paraquat does pass the blood–brain barrier.[25] A slow-moving degeneration of the DAergic neurons in the brain SNpc[26] and the VTA [27] has been observed following systemic (i.p or other means), chronic administration of paraquat (up to 24 weeks). This results in delayed deficits in DAergic transmission that mimic the early presymptomatic stages of PD.[28,29]Mice exposed systemically to this herbicide show decreased motor as well as an activity of dose dependent TH-positive cell loss striatal fibres and SNpc neurons.[30]The capacity of the Paraquat (and/or Maneb) model to promote the development of LB-like inclusions harbouring a-synuclein is one of its benefits .[31] The only agricultural pesticide with a proven adverse effect on the dopamine system is paraquat. Maneb, which is utilised in an area where paraquate is also used, has been demonstrated to reduce locomotor activity and enhance the effects of MPTP.[32] increased levels of synuclein in specific DA neurons within the SNpc, as well as the appearance of Lewy bodies in those DA neurons. In light of this, paraquat has a role in PD research because, should the aforementioned observations be verified, it may enable us to explore how Lewy bodies develop in DA neurons as well as the function of synuclein in PD. The outcomes of this model, however, are inconsistent and vary in terms of DAergic cell death, striatal DA depletion, and behaviour.[33]

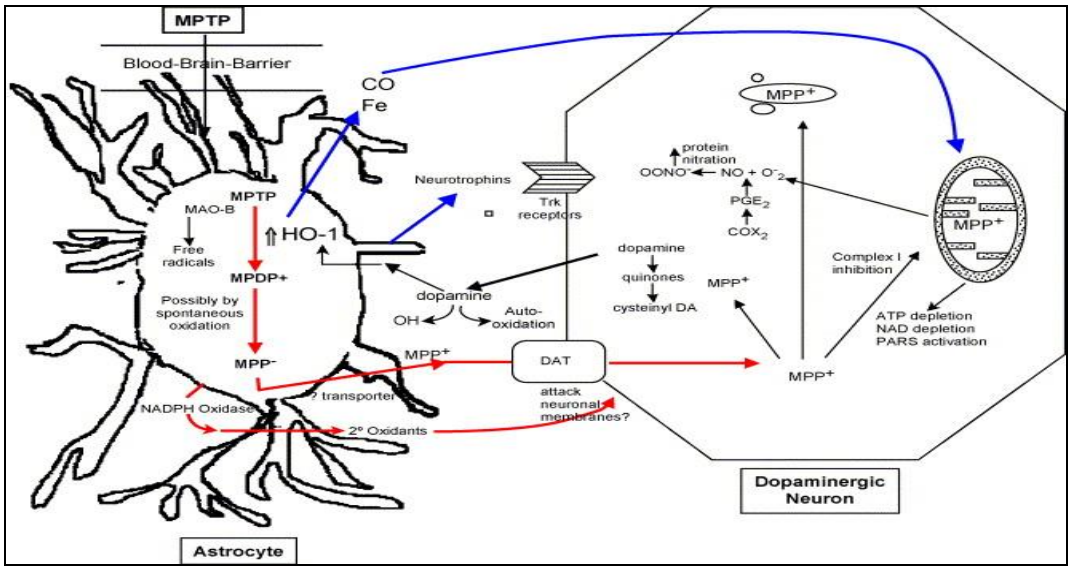

Figure 1: The mechanism of MPTP action in the nigrostriatal system

Rotenone:- The rotenoid neurotoxic family includes rotenone, a herbicide, insecticide, and piscicide . It is found in nature tropical plants like the j'cama vine (Pachyrhizus erosus) and several Derris genus leguminous plants. The rotenone model demonstrates that systemic complex 1 inhibition can cause the symptoms of PD.[34] Nearly all PD symptoms, including the loss of SNcDAergic neurons, nigrostriatal DAergic denervation, behavioural changes, inflammation, LB-like inclusions containing a-synuclein and ubiquitin, oxidative stress, and digestive issues, are replicated in the rotenone model.[35] The Rotenone model demonstrates that PD symptoms can result in extreme rigidity, tremor, akinesia, and flexed posture. Rotenone, however, has a high mortality rate in experimental animals and generates variable, challenging-to-replicate DAergic harm. Rotenone has been used to test pharmacological and genetic therapy intended to protect dopamine cells.The challenge with using rotenone as a Parkinson's disease model is that, while increasing DA oxidation, there is little evidence that it depletes DA in the nigrostriatal pathway.Rotenone therapy produces motor and non-motor Parkinson's disease (PD)-like symptoms as well as central and peripheral neuropathological characteristics [36]

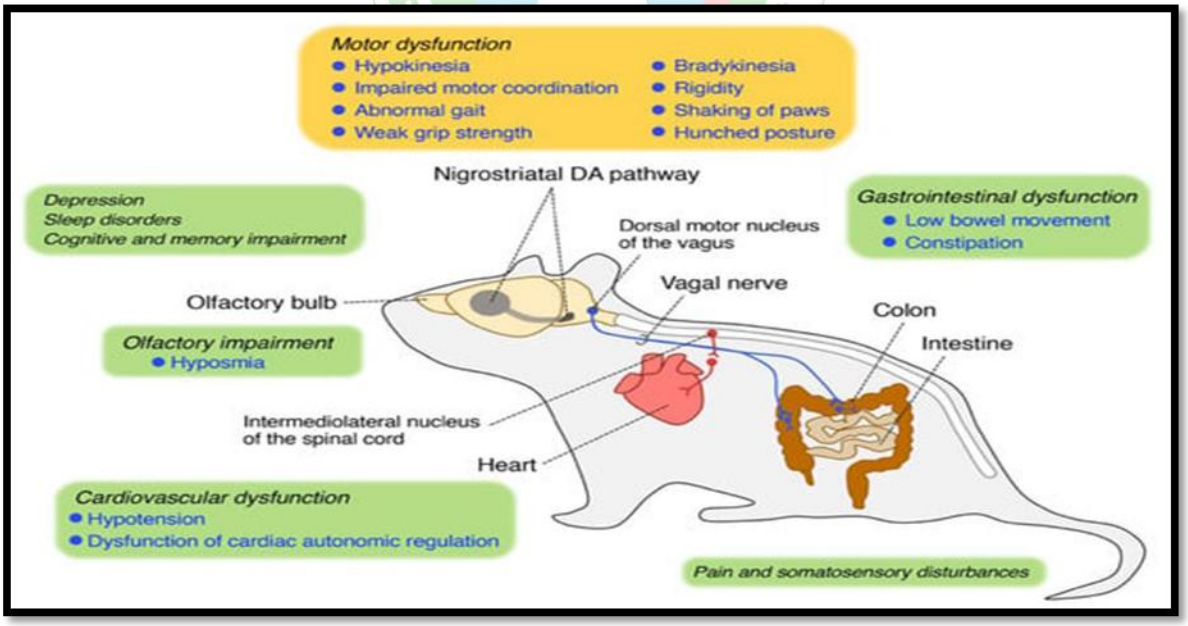

Figure 2: Rotenone model

Genetic Model: -Autosomal dominant or recessive inheritance genetic alterations account for 20% of PD cases. [38]. Nonetheless, these examples are extremely fascinating because the cause of disease is at least partially characterised, and these studies provide justification for creating animal models with comparable mutations. Synuclein is the first gene that has been conclusively related to familial Parkinson's disease [39]. Many other family PD-related genes connected to autosomal dominant or recessive inheritance types of PD were further discovered after this finding in 1997.[40] More than 25 genetic risk factors, including 15 causative genes, have been discovered so far,

and they are categorised as "PARK" and "non-PARK" (>20) loci/genes . A-synuclein, PARK1 and 4, PRKN (parkin RBR E3 ubiquitin protein ligase, PARK2), PINK1 (PTEN-induced putative kinase 1, PARK6), DJ-1 (PARK7), and LRRK2 (leucine rich repeat kinase 2, PARK8) are some of them that have been modelled in mice and rats , while others are still being developed.[41] Among the different models of Parkinsonian neurodegeneration, protein aggregation, dysfunction of the mitochondria, dysfunction of the secretory pathway organelles, and oxidative stress are common variables. (Edward d). If the inheritance pattern of PD-linked genes in humans indicates a dominant transmission, these genes are typically produced as transgenes in heterologous organisms. These non-mammalian PD models' well-characterized genetics provide a special benefit for the human model over the mouse for the quick discovery of modifiers that could shed light on crucial disease pathogenesis pathways, insights into which could aid the subsequent development of novel treatments.[42]

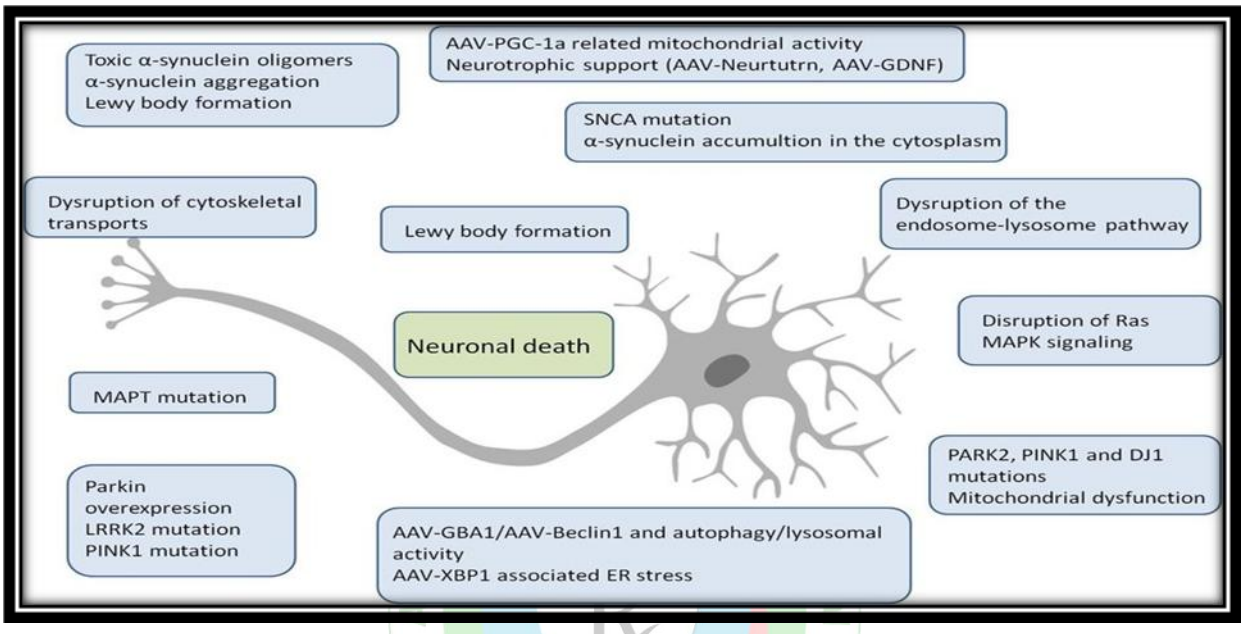

Figure 3: Parkinsonism's genetic origins and disease-related genetic pathways**.**

Alpha-synuclein: - The protein -synuclein, which is 140 length of an amino acid and is widely distributed throughout neurons, is notably enriched in pre-synaptic terminals[43]]Since point mutations in the -synuclein gene were discovered to be the cause of rare forms of familial PD , genetic locus multiplication and genetic locus duplication -synuclein has been PD genetic's primary area of concern research.[44] addition, it was found that ubiquitinated aggregates of -synuclein. The idea that -synuclein aggregation is a key factor in sporadic PD has been strengthened by the discovery that are a substantial one of the Lewy bodies in postmortem PD brains.[45] The original transgenic mouse version that overexpresses human -synuclein in its wild type was created by Masliah et al. In the neocortex, hippocampus, and SN of these mice, neuronal inclusions accumulated over time and stained positively with antibodies to -synuclein and ubiquitin. These inclusions don't, however, have the fibrillar makeup that often distinguishes LBs. Furthermore, these mice don't appear to have lost any DA neurons. The degeneration pattern is different from the severe DA cell loss reported in Parkinson's disease (PD), despite the highest-expressing line showing considerable degeneration of THpositive nerve terminals inside the striatum and accompanied with motor impairment on a rotarod. Using viral vectors to over-express PD-linked genes is a valid alternative and crucial method of modelling PD in rodents. So, it appears that for -synuclein to exhibit its toxicity in DA neurons, at least in rodents, a threshold expression level (achieved by viral administration) or some alterations (achieved by truncation or double mutation) are required. Interestingly, an RNAi genome-wide screening indicated suppressor roles for a number of age-related genes in synuclein-mediated inclusion development, including sir-2.1/SIRT1 and lagr-1/LASS2.

Parkin:- Parkinson's disease has an autosomal recessive variant that is brought on by the parkin gene. In 1998, the gene was identified. The PARK2 gene, found on the 6q chromosome, encodes the Parkin (Parkinson juvenile disease protein 2) is a 52 kDa (426 amino acid) enzyme protein.. It is a crucial component of the ubiquitin-proteasome system that controls the breakdown of proteins. Parkin is initially found in the cytoplasm, but when a prolonged depolarization takes place, it is translocated to the mitochondrial surface and causes the degradation of a number of membrane proteins that are potential mitophagies candidates. The integrity of the cellular mitochondria depends on parkin. Proteins that are misfolded and aggregated as a result of the parkin mutation build up and degrade mitochondria. These alterations play a well-known part in the patho mechanism of neurodegenerative disorders. For a long time, it was widely believed that Parkinson's disease has no cure. sporadic disease with a hereditary component .Shortly after the identification of the -synuclein gene as a familial PD-linked gene, it was found that parkin gene mutations cause autosomal recessive juvenile parkinsonism.[46] Parkin is a ubiquitin E3 ligase, and it is considered that both familial and sporadic Parkinson's

disease (PD) are influenced by the loss of its enzymatic activity. At least some of the parkin-related Parkinson's disease cases may have parkin as a relevant pathogenic factor[47]

PINK1:- It has been demonstrated that the mitochondrially focused serine/threonine kinase PINK1 guards cells against oxidative stress-induced apoptosis.[48]The PINK1 protein has mutations related with PD throughout, however the majority are concentrated in the kinase domain. Italian families with autosomal recessive and early-onset PD cases were where mutations (missense or nonsense in the PINK1 gene were first discovered.[49] In addition to having mildly lower levels of brain DA as they age, PINK1/mice have moderate mitochondrial impairments, greater susceptibility to oxidative stress, and a progressive decline in weight and locomotor activity. In general, neither LB-like aggregates nor striatonigral DAergic system alterations are visible in PINK1/mice. Overall, PINK1 models do not result in other PD-related abnormalities or functional disruption of the nigrostriatal DAergic neurons.[50]

DJ1:- Numerous roles are performed by the protein encoded by the DJ-1 gene (PARK7), including mitochondrial control, protease activity, and transcriptional regulation Missense DJ-1 mutations are related to early-onset and autosomal recessive PD.[51] Mutations of DJ-1 associated with familial parkinsonism generally occur in a recessive fashion.[52]. No SNc DAergic neurons are lost in DJ-1/mice, but they do exhibit altered corticostriatal synaptic plasticity, decreased striatal DA release, and a reduced sensitivity to D2 auto receptor activation. In a different model, mice with DJ-1 loss were obtained using the "gene trap" technique. These mice displayed changes in object recognition along with upregulated mitochondrial respiratory activity, fewer DAergic neurons in the VTA, but no decreased DAergic terminals in the striatum, suggesting the involvement of this protein in the early phase non-motor symptoms of Parkinson's disease and the existence of compensatory mechanisms.[53]

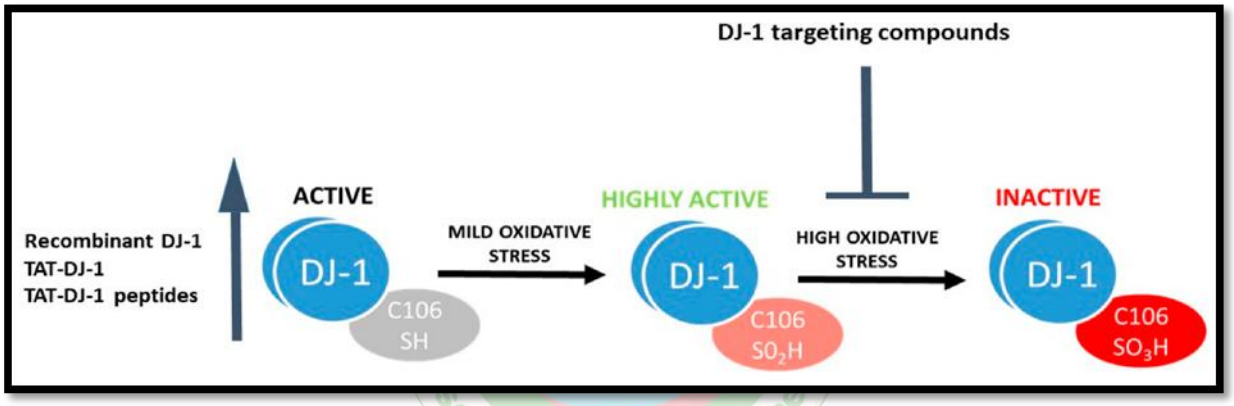

Figure 4: Targeting DJ-1 as therapeutic approach for PD

Table: Symptomatic Treatment of Parkinson Disease**:** -[54-60]

Drug	Mechanism of Action	Indication (Motor and Non-Motor Symptoms)	Adverse Effects
Anticholinergics Benztropine, trihexyphenidyl	are drugs that block and inhibit the activity of the neurotransmitter acetylcholine (ACh) at both central and peripheral nervous system synapses.	Tremor	Hallucinations, nausea, dry mouth, blurred vision, urinary retention, and constipation
Carbidopa/levodopa	The blood-brain barrier can be crossed by levodopa. (BBB). Both the CNS and the peripheral areas of the body convert levodopa to dopamine. Levodopa is frequently used along to boost its absorption and lessen its adverse effects. (such as carbidopa). Levodopa can can more readily cross the BBB cross to dopamine-decarboxylase inhibitors because they stop levodopa from being converted to dopamine in the peripheral area. It produces dopamine when converted, which then stimulates postsynaptic dopaminergic receptors to make up for the loss of endogenous dopamine.	The most successful drug for treating Parkinson's disease symptoms is levodopa, which is still used; Most effective at controlling disability.	Orthostatic hypotension, sedation, disorientation, dystonia, and psychosis symptoms.
COMT inhibitors Entacapone, Tolcapone	Levodopa is prevented from degrading in the by preventing the enzyme, the peripheral nervous system catechol-o-methyl-transferase (COMT), which enables a larger quantity to cross the blood-brain barrier.	Early modest signs, only motor signs frequently an additional drug medication	Dark-coloured urine, a worsening of levodopa's side effects, diarrhoea, and hepatotoxicity
Dopamine agonists Bromocriptine Pergolide Pramipexole Ropinirole	Dopamine agonists bypass the need for metabolic conversion, storage, and release by acting directly on postsynaptic dopamine receptors. Dopamine agonists increase the impact of dopamine by acting on dopamine receptors.	Motor symptoms Useful for the initial treatment of parkinsonism and as adjunct therapy in	Hallucinations, nausea edema, fibrosis of cardiac valves, lung, and retroperitoneum;

		patients taking levodopa	retroperitoneal, pulmonary fibrosis, hypotension
MAO-B inhibitors Selegiline Rasagaline	Dopamine is metabolised by the enzyme monoamine oxidase B (MAO-B), which produces 3,4-dihydroxyphenylacetic acid (DOPAC), which is then converted into Homvanillic acid by the enzyme catechol-O-Methyltransferase (COMT).To reduce dopamine metabolism and consequently boost levels of dopamine in the brain, MAO-B inhibitors have been added to the therapy regimen for PD treatment, which reduces motor symptoms. Selegiline and rasagiline, both irreversible MAO-B inhibitors.	as adjuvant therapy . Early mild symptoms, all motor symptoms	Weight loss, hypotension, dry mouth, drug interactions with other MAO inhibitors/tyramine
NMDA receptor inhibitor Amantadine	Amantadine's indirect dopamine-releasing activity and direct activation of dopamine receptors are most likely to play significant roles in the relief of Parkinson's symptoms.	Useful for treating akinesia, rigidity, tremor, dyskinesia.	Nausea, hypotension, hallucinations, confusion, edema
Adenosine receptor antagonist	Adenosine A2A receptors and D2 dopaminergic receptors are co-localized in the striatum, suggesting that adenosine and dopamine may interact antagonistically.	Motor (Dyskinesia) and non-motor treatment (anxiety ,depression ,cognitive impairment)	Nausea, Dizziness Hallucinations Diarrhoea Insomnia, Decreased appetite
Beta -Blocker Propranolol	The precise process underlying propranolol's antitremor effects is still being studied. The effectiveness of propranolol in treating ET is most likely due to the blocking effects of peripheral noncardiac beta-2 receptors found in the muscle spindles, despite the fact that it is generally recognised that ET is generated within the central nervous system (CNS). A peripheral mechanism for this class of drugs is further supported by the fact that less lipophilic beta blockers are also efficient at suppressing ET. Epinephrine increases the sensitivity of muscle spindles, synchronization, and improved reflex activity.	Tremor	Fatigue, dizziness, and depression
Anti-seizure Primidone Topiramate Gabapentin	Excitation can be inhibited by affecting excitatory synaptic transmission (e.g., glutamate AMPA and NMDA receptors and synaptic vesicle protein 2A) or innate excitability mechanisms in excitatory neurons (e.g., inhibition of sodium and calcium channels). greater availability of gamma-aminobutyric acid (GABA), greater activation of GABAA receptors, inhibitory mediators in seizure-relevant cortical regions, and modulation of the voltage-gated potassium channel of the Kv7 all contribute to the enhancement of inhibition.	Tremor, Seizure, Anxiety, Epilepsy	Ataxia, dizziness, blurred vision, headache, vertigo,
Tranquilizer Chlorazepam Chlordiazepoxide	GABAergic neurotransmission is enhanced by benzodiazepines. They attach to the GABAA receptor complex directly, and by increasing GABA binding, their presence causes a greater influx of chloride ions. This causes the cell membrane to become hyperpolarized, which inhibits the action potential's ability to fire.	anticonvulsant, muscle relaxant, and li antitremorgenic effects.	Drossiness, Light headedness, confusion, Muscle weakness, Memory problem

REFERENCES:

1. Wooten GF, neurochemistry and neuropharmacology of Parkinson disease in :walts RL Koller W eds: Movement disorder neurological principle and practice Newyprk and MC graw Hill 1997 p 153-160.
2. Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A.-E., & Lang, A. E. Parkinson disease. Nature Reviews Disease Primers, 2017; 3(1):1–21. https://doi.org/10.1038/nrdp.2017.13.
3. Hornykiewicz O. The discovery of dopamine deficiency in the parkinsonian brain. J Neural TransmSuppl 2006; 9.
4. Björklund, A., & Dunnett, S. B. Dopamine neuron systems in the brain: An update. Trends in Neurosciences, 2007; 30(5):194–202. https://doi.org/10.1016/j.tins.2007.03.006.
5. Barré-Sinoussi, F., &Montagutelli, X. Animal models are essential to biological research: Issues and perspectives. Future Science OA, 1(4), FSO63. https://doi.org/10.4155/fso.15.636.Parkinson's disease. Mov Disord 2011; 26 .
6. Malaiwong, N., Chalorak, P., Jattujan, P., Manohong, P., Niamnont, N., Suphamungmee, W., Sobhon, P., & Meemon, K. Anti Parkinson activity of bioactive substances extracted from Holothurialeucospilota. Biomedicine & Pharmacotherapy 2019; 109:1967–1977. https://doi.org/10.1016/j.biopha.2018.11.063.
7. Dawson TM, Dawson VL. Molecular pathways of neurodegeneration in Parkinson's disease. Science 2003; 302(5646):819–22.
8. Gubellini P, Picconi B, Di FM, Calabresi P. Downstream mechanisms triggered by mitochondrial dysfunction in the basal ganglia: from experimental models to neurodegenerative diseases. Biochim Biophys Acta 2010; 1802(1):151–61.
9. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron 2003; 39(6):889–909.
10. Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem 1990; 54(3):823–7.
11. Ungerstedt U. 6-Hydroxy-dopamine induced degeneration of central monoamine neurons. Eur J Pharmacol 1968; 5(1):107–10.
12. Porter CC, Totaro JA, Stone CA. Effect of 6- hydroxydopamine and some other compounds on the concentration of norepinephrine in the hearts of mice. J Pharmacol Exp Ther1963; 140:308–16.
13. Blum D, Torch S, Lambeng N, Nissou M, Benabid AL, Sadoul R, et al. Molecular pathways involved in the neurotoxicity of 6-OHDA,

dopamine and MPTP: contribution to the apoptotic theory in Parkinson's disease. Prog Neurobiol 2001; 65(2):135–72.

14. Faull RL, Laverty R,changes in dopamine level in striatum following lesion in substantia nigra Exp neurol 1969:23:332-340.
15. Lee CS, Sauer H, Bjorklund A. Dopaminergic neuronal degeneration and motor impairments following axon terminal lesion by instrastriatal 6-hydroxydopamine in the rat. Neuroscience 1996; 72:641–53.
16. Alves da Costa C, Dunys J, Brau F, Wilk S, Cappai R, Checler F. 6-Hydroxydopamine but not 1-methyl-4-phenylpyridinium abolishes alpha-synuclein anti-apoptotic phenotype by inhibiting its proteasomal degradation and by promoting its aggregation. J Biol Chem 2006; 281:9824–31.
17. Ballard PA, Tetrud JW, Langston JW. Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP): seven cases. Neurology 1985; 35(7):949–56.
18. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidineanalog synthesis. Science 1983; 219(4587):979–80.
19. Cui M, Aras R, Christian WV, Rappold PM, Hatwar M, Panza J, et al. The organic cation transporter-3 is a pivotal modulator of neurodegeneration in the nigrostriatal dopaminergic pathway. Proc Natl Acad Sci U S A 2009; 106:8043–8.
20. Hantrayep ,VarastetM, Peschanski M, Riche D, Cesaao P, Wiler JC , Maziere M, stable parkinsonian syndrome and uneven loss of striatal dopamine fibres following chronic MPTP administration in baboons neuroscience 1993:53:179-178.
21. Chiueh CC, Markey SP, Burns RS, Johannessen JN, Jacobowitz DM, Kopin IJ. Neurochemical and behavioral effects of 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) in rat, guinea pig, and monkey. Psychopharmacol Bull 1984; 20:548–53.
22. Smeyne RJ, Jackson-Lewis V. The MPTP model of Parkinson's disease. Brain Res Mol Brain Res 2005; 134(1):57–66.
23. Ranjita betarbet,ToddB,Sherer et al animal models of Parkinson disease bioassay 24:308-318 2002 wiley periodicals .inc DOI 10:1002/bies .10067.
24. Berry C, La Vecchia C, Nicotera P. Paraquat and Parkinson's disease. Cell Death Differ 2010; 17:1115–25.
25. Brooks AL Chadwick CA GelbardHA, Cloryceshata DA, Fedroff HJ Paraquate elicited neurobehavioral syndrome caused by dopaminergic neuron loss,brain res 1999:823:1-10.
26. Ossowska K, Wardas J, Smialowska M, Kuter K, Lenda T, Wieronska JM, et al. A slowly developing dysfunction of dopaminergic nigrostriatal neurons induced by long-term paraquat administration in rats: an animal model of preclinical stages of Parkinson's disease? Eur J Neurosci 2005; 22(6):1294–304.
27. Ossowska K, Smialowska M, Kuter K, Wieronska J, Zieba B, Wardas J, et al. Degeneration of dopaminergic mesocortical neurons and activation of compensatory processes induced by a long-term paraquat administration in rats: implications for Parkinson's disease. Neuroscience 2006; 141(4):2155–65.
28. Day BJ, Patel M, Calavetta L, Chang LY, Stamler JS. A mechanism of paraquat toxicity involving nitric oxide synthase. Proc Natl Acad Sci U S A 1999; 96(22):12760–5.
29. Brooks AI, Chadwick CA, Gelbard HA, Cory-Slechta DA, Federoff HJ. Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. Brain Res 1999; 823(1–2):1–10.
30. Thiruchelvam M, Brockel BJ, Richfield EK, Baggs RB, Cory-Slechta DA. Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? Brain Res 2000; 873:225–34.
31. Manning-Bog AB, McCormack AL, Li J, Uversky VN, Fink AL, Di Monte DA. The herbicide paraquat causes upregulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. J Biol Chem 2002; 277(3):1641–4.
32. Takahashi RN, Rogerio R, Zanin M. Maneb enhances MPTP neurotoxicity in mice. Res Commun Chem Pathol Pharmacol 1989; 66(1):167–70.
33. Miller GW. Paraquat: the red herring of Parkinson's disease research. Toxicol Sci 2007; 100(1):1–2.
34. Greenamyre JT, Betarbet R, Sherer TB. The rotenone model of Parkinson's disease: genes, environment and mitochondria. Parkinsonism RelatDisord 2003; 9(Suppl. 2):S59–64.
35. Greenamyre JT, Cannon JR, Drolet R, Mastroberardino PG. Lessons from the rotenone model of Parkinson's disease. Trends Pharmacol Sci 2010; 31(4):141–2.
36. Degli Esposti M inhibitor of NABH ubiquinone reductase overview biochimbiosphy acta 1999:1364:222:235.
37. Verstraeten A, Theuns J, Van BC. Progress in unraveling the genetic etiology of Parkinson disease in a genomic era. Trends Genet 2015; 31(3):140–9.
38. M.H. Polymeropoulos, C. Lavedan, E. Leroy, S.E. Ide, A. Dehejia, A. Dutra, B. Pike, H. Root, J. Rubenstein, R. Boyer, E.S. Stenroos, S. Chandrasekharappa, A. Athanassiadou, T. Papapetropoulos, W.G. Johnson, A.M. Lazzarini, R.C. Duvoisin, G. Di Iorio, L.I. Golbe, R.L. Nussbaum, Mutation in the alphasynuclein gene identified in families with Parkinson's disease, Science 276 (1997) 2045–2047.
39. T. Kitada, S. Asakawa, N. Hattori, H. Matsumine, Y. Yamamura, S. Minoshima, M. Yokochi, Y. Mizuno, N. Shimizu, Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism, Nature 392 (1998) 605–608.
40. Kitada T, Tong Y, Gautier CA, Shen J. Absence of nigral degeneration in aged parkin/DJ-1/PINK1 triple knockout mice. J Neurochem 2009;1 11(3):696–702.
41. K.-L. Lim, C.-H. Ng Genetic models of Parkinson disease Biochimical et Biophysica Acta 1792 (2009) 604–615.
42. D.D. Murphy, S.M. Rueter, J.Q. Trojanowski, V.M. Lee, Synucleins are developmentally expressed, and alpha-synuclein regulates the size of the presynaptic vesicular pool in primary hippocampal neurons, J. Neurosci. 20 (2000) 3214–3220.
43. Verstraeten A, Theuns J, Van BC. Progress in unraveling the genetic etiology of Parkinson disease in a genomic era. Trends Genet 2015; 31(3):140–9.
44. P.Gubellini, P. Kachidian, Animal models of Parkinson's disease: An updated overview Revue neurologique (2015), http://dx.doi.org/10.1016/j.neurol.2015.07.011.
45. Kah-Leong Lim , Chee-Hoe Ng,Genetic models of Parkinson disease Biochimica et Biophysica Acta 1792 (2009) 604–615.
46. Dawson TM, Dawson VL. The role of parkin in familial and sporadic Parkinson's disease. Mov Disord 2010; 25(Suppl. 1):S32–9.
47. Lazarou M, Narendra DP, Jin SM, Tekle E, Banerjee S, Youle RJ. PINK1 drives Parkin self-association and HECT-like E3 activity upstream of mitochondrial binding. J Cell Biol 2013; 200(2):163–72.
48. Valente EM, bou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 2004; 304(5674):1158–60.
49. Oliveras-Salva M, Macchi F, Coessens V, Deleersnijder A, Gerard M, Van der PA, et al. Alpha-synuclein-induced neurodegeneration is exacerbated in PINK1 knockout mice. Neurobiol Aging 2014; 35(11):2625–36.
50. Hedrich K, Djarmati A, Schafer N, Hering R, Wellenbrock C, Weiss PH, et al. DJ-1 (PARK7) mutations are less frequent than Parkin (PARK2) mutations in early-onset Parkinson disease. Neurology 2004; 62(3):389–94.
51. Bonifati, P. Rizzu, M.J. Van Baren, O. Schaap, G.J. Breedveld, E. Krieger, M.C. Dekker, F. Squitieri, P. Ibanez, M. Joosse, J.W. Van Dongen, N. Vanacore, J.C. Van Swieten, A. Brice, G. Meco, C.M. Van Duijn, B.A. Oostra, P. Heutink, Mutations in the DJ-1 gene associated with autosomal recessive early-onset Parkinsonism, Science 299 (2002) 256–259.

52. 53.Pham TT, Giesert F, Rothig A, Floss T, Kallnik M, Weindl K, et al. DJ-1-deficient mice show less TH-positive neurons in the ventral tegmental area and exhibit non-motoric behavioural impairments. Genes Brain Behav 2010; 9(3):305–17.

53. Shobha S. Rao, M.D., Laura A Parkinson's Disease: Diagnosis and Treatment December 2006; 15 (74), Number 12 www.aafp.org/afp American Family Physician.

54. B. S., & Lang, A. E. Parkinson disease: An update. American Family Physician, 2014; 87(4):267-273 and Connolly.

55. Kristina Terzakis, SN Parkinson disease Volume 34 | Number 6 www.homehealthcarenow.org 2016 Wolters Kluwer Health.

56. J. Michael Ellis a, Matthew J. Fell Current approaches to the treatment of Parkinson's Diseas Bioorganic & Medicinal Chemistry Letters 2017; 27:4247–425.

57. Hedera et al. Pharmacotherapy of Essential Tremor. Journal of Central Nervous System Disease 2013; 5:43–55 doi: 10.4137/JCNSD.S6561.

58. Shah B (2017) Essential Tremor: A Comprehensive Overview. J Neurol Disord 5: 343. doi:10.4172/2329-6895.1000343.

59. W. Oertel and J. B. Schulz International Society for Neurochemistry, J. Neurochem. (2016) 10.1111/jnc.13750.