MASTER OF SCIENCE (BIOTECHNOLOGY) [DIVYA YADAV] 2022

IN SILICO ANALYSIS OF ANTIHISTAMINE DRUGS AS NEUROPROTECTANTS TARGETING DOPAMINE D2-LIKE RECEPTORS IN PARKINSON'S DISEASE

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF

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IN

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Submitted by:

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CANDIDATE'S DECLARATION

I, **Divya Yadav**, (Roll No.: 2K20/MSCBIO/06) hereby certify that the work which is presented in the Major Project entitled **"In silico analysis of antihistamine drugs as neuroprotectants targeting dopamine D2-like receptors in Parkinson's disease"** in fulfilment of the requirement for the award of Degree of Masters of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi is an authentic record of my own work, carried during a period from 10-June-2021 to 01-May-2022, under the supervision of **Prof. Pravir Kumar.**

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other university. This work has been communicated in Scopus indexed journal and conference with the following details:

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CERTIFICATE

To the best of my knowledge, the above work entitled **"In silico analysis of antihistamine drugs targeting Dopamine D2-like receptors in Parkinson's disease"** has not been submitted in part or full for any Degree or Diploma to this University or elsewhere. I further certify that the publication and indexing information given by the student is correct.

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Restoration and targeting of aberrant neurotransmitters in Parkinson's disease therapeutics

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ABSTRACT

Neurotransmitters are considered as a fundamental regulator in the process of neuronal growth, differentiation and survival. Parkinson's Disease (PD) occurs due to extensive damage of dopamine-producing neurons; this causes dopamine deficits in the midbrain, followed by the alternation of various other neurotransmitters (glutamate, GABA, serotonin, etc.). It has been observed that fluctuation of neurotransmission in the basal ganglia exhibits a great impact on the pathophysiology of PD. Dopamine replacement therapy, such as the use of L-DOPA, can increase the dopamine level, but it majorly ameliorates the motor symptoms and is also associated with long-term complications (for e.g., LID). While the non-dopaminergic system can efficiently target non-motor

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Parkinson's Disease: An Overview and Role of Glutamate and its Receptors

Glutamate receptor based therapy as an alternate way to treat Parkinson's

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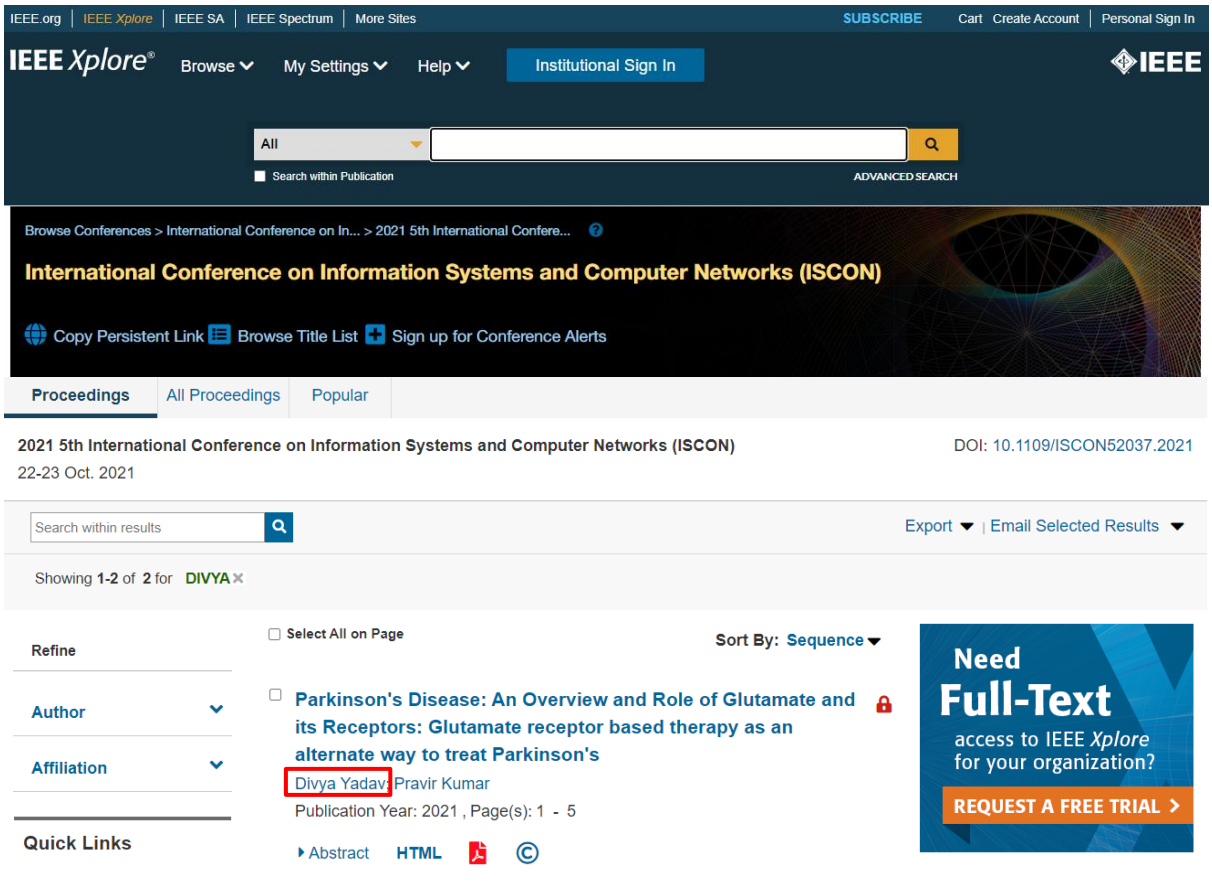
***Abstract*—Among several neurodegenerative disorders, Parkinson's is one of the utmost widespread diseases, occur due to the degeneration of the dopaminergic neurons in the region of midbrain which is identified by motor signs like tremor & bradykinesia; non-motor features (like impaired vision, depression, sleeping disorders). Currently, there is no treatment available that can cure PD. It is possible that ligands of glutamate receptor may decelerate the progression of PD via delaying progressive degeneration of dopamine neuron as glutamate is one of the key regulators of basal ganglia functioning & its level increases in PD patients. In addition, alteration of glutamate receptor during the disease and the anti-parkinsonian process has been reported. Reversal of**

Parkinson Disease Association (APDA), around 1 million people in the U.S. are having PD and more than 10 million individuals worldwide are suffering from PD. Still there is no cure available for PD but some drugs are there in the market to treat the symptoms & slow down the progression of disease. Selection of drug must be done after estimating both the short-term benefits and long-term consequences. Another factor while selecting the drug is to consider patient-specific factors, for example level of disability, functional & chronologic age, drug tolerance and expected efficacy [3]. Before the motor symptoms turn up, around 50-70% neurons in SNc are degenerated. Current drugs used by PD patients



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ABSTRACT

Among several neurodegenerative disorders, Parkinson's is one of the utmost widespread diseases, occur due to the degeneration of the dopaminergic neurons in the region of midbrain which is identified by motor signs like tremor & bradykinesia; non-motor features (like impaired vision, depression, sleeping disorders). Currently, there is no treatment available that can cure PD. However, there is an imbalance between signaling pathway in the basal ganglia circuit. The direct pathway is downregulated and mediated via dopamine D1-like receptors. In contrast, the indirect pathway is upregulated and this is mediated via dopamine D2-like receptors. Using dopamine D2-like receptors antagonists, PD symptoms can be ameliorated. Increased histaminergic signaling has been observed in PD.

Herein, we want to analyze the interaction between approved antihistamine drugs with dopamine D2-like receptors. We curated a list of 58 approved antihistamine drugs to analyze their affinity with dopamine D2-like receptors as an inhibitor. Literature indicates a substantial correlation between the antihistamines and dopamine D2-like receptors. Thus, targeting these drugs might regulate the disrupted indirect pathway in the basal ganglia circuit.

Through molecular docking analysis, we identified that bilastine, a highly potent and selective inhibitor of histamine H1 receptor shows high affinity with dopamine D2-like receptors and might inhibit the aberrant signaling cascade of indirect pathway and upregulated histaminergic signaling simultaneously. Further studies are required to determine the action.

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LIST OF ABBREVATIONS

PD	Parkinson's Disease
PET	Positron Emission Tomography
LHb	Lateral Habenula
APDA	American Parkinson Disease Association
LID	Levodopa-Induced Dyskinesia
GABA	Gamma-Aminobutyric Acid
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazole Propionic Acid Receptor
SPECT	Single Photon Emission Computed Tomography
FDA	Food and Drug Administration
SNc	Substantia Nigra Pars Compacta
MAO-B	Monoamine Oxidase B
L-Dopa	Levodopa
RLS	Restless Legs Syndrome
Str	Striatum
BDNF	Brain-derived Neurotrophic Factor
GPe	Globus Pallidus Externa
MRI	Magnetic Resonance Imaging
LGP	Lateral Globus Pallidus
CREB	cAMP-Response Element Binding Protein
NMDAR	N-methyl-D-aspartate Receptor
CT	Computed Tomography
ERK	Extracellular Signal-Regulated Kinase
Gpi	Internal Globus Pallidus
6-OHDA	6-hydroxydopamine

CNS	Central Nervous System
LDAEP	Loudness Dependence of the Auditory Evoked Potential
5-HT	Serotonin
CINs	Cholinergic Interneurons
cAMP	Cyclic Adenosine Monophosphate
PDD	Parkinson's Disease Dementia
HA	Histamine
PI3K	Phosphoinositide 3-Kinase
MAPK	Mitogen-Activated Protein Kinase
Aβ	Amyloid beta
eEF2	Eukaryotic Elongation Factor 2
nAChR	Alpha-5 Nicotinic Acetylcholine Receptor
TNF-α	Tumour Necrosis Factor Alpha
COMT	Catechol-O-Methyltransferase
MDD	Major Depressive Disorder
SNr	Substantia Nigra Pars Reticulata
PDB	Protein Data Bank
AD	Alzheimer’s Disease
HD	Huntington’s Disease
STN	Subthalamic Nucleus
ALS	Amyotrophic Lateral Sclerosis

CHAPTER – 1

INTRODUCTION

1.1 BACKGROUND

Among several neurodegenerative disorders, Parkinson's is one of the utmost widespread diseases, with a high prevalence rate in the male gender. PD is a neurological disorder with early prominent death of pigmented dopaminergic neurons in the substantia nigra pars compacta (SNc), region of the midbrain which leads to dopamine deficit along with accumulation of intraneural inclusion, known as Lewy bodies that are composed of a protein called α-synuclein aggregates [1], [2]. And the movement disorder is caused by mainly due to the deficiency of dopamine within the basal ganglia region [2] as shown in **Fig. 1.1** [3]. Furthermore, the striatum collects synaptic input from all the cortical regions, whereas the excitatory glutamatergic signal is regulated by the thalamic region [4]. And in the striatal region, the efficacy of synaptic transmission is regulated by different neurotransmitter systems, including glutamatergic, GABAergic, cholinergic, serotonergic, noradrenergic [5]–[7].

For instance, PD symptoms can be ameliorated upon administration of anticholinergic and anti-histamine drugs, and this indicates that apart from the dopaminergic deficit, other neurotransmitter systems are also affected [8], [9]. The pre-synaptic D4 receptors in the lateral habenula (LHb) exhibit a vital role in the modulation of PD-associated depression [10], agonist A412997 and antagonist L741742 of D4 receptors were injected in SNc sham-lesioned and SNc lesioned rats with different doses, and it was determined that at high concentration firing rate of LHb neurons and neurotransmission emittance are changed in both animal models whereas at low concentration changes occurred in the firing rate and release of neurotransmitters (Dopamine, Glutamate, and GABA in the LHb) through the GABAergic rostromedial tegmental nucleus only in the SNc sham-lesioned.

In PD, increased histaminergic innervation is present at the superior colliculus of SN with altered morphology and release of HA has many effects, such as activation of microglia and astrocytes [11]. During the evolution, it has been observed that the central HA system is well conserved [12]. Histaminergic neurons are present in the hypothalamus at the tuberomammillary nucleus, and they are involved in various functions such as memory

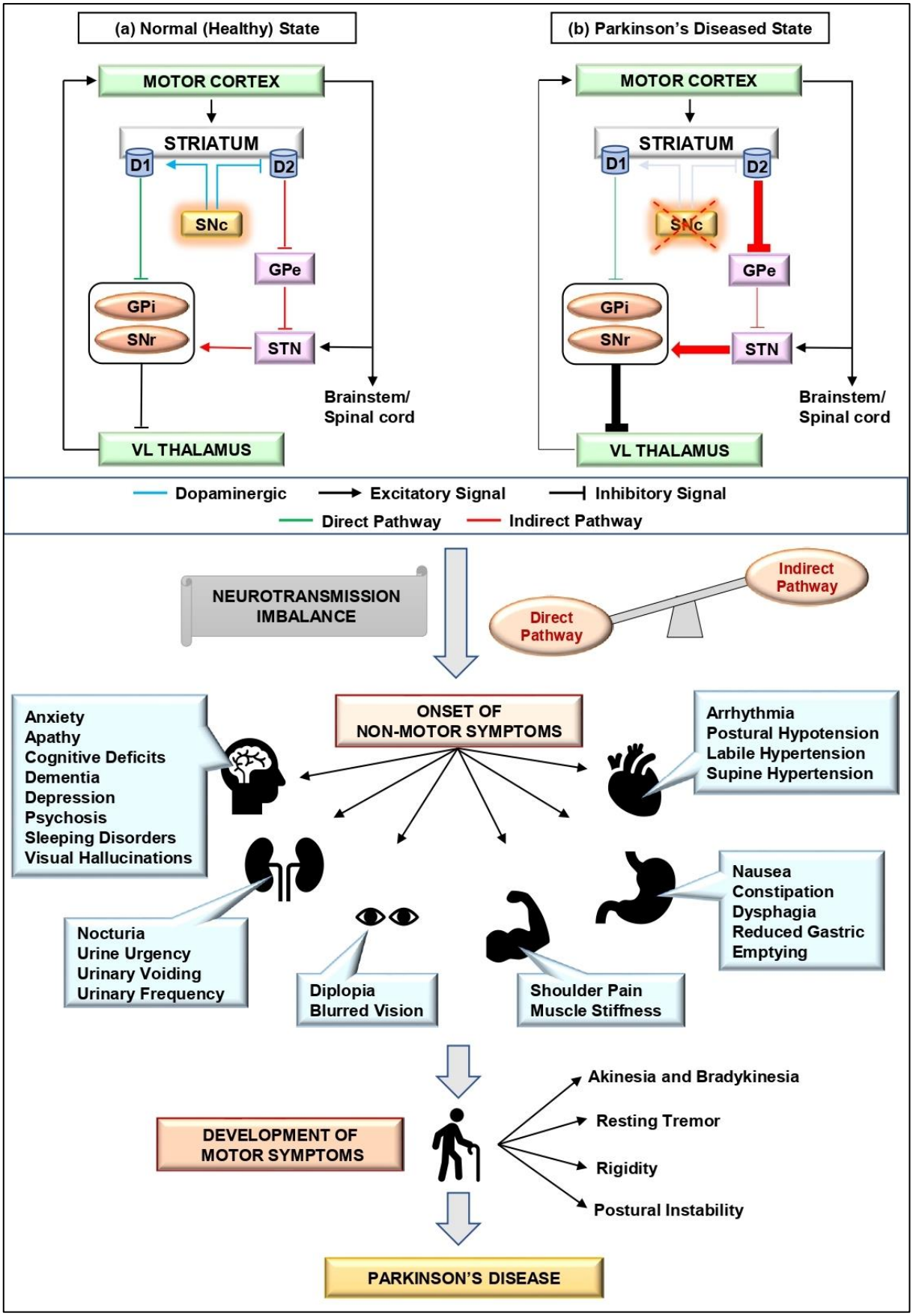


Figure 1.1: Alternation in basal ganglia circuit and development of Parkinson's Disease.

process, cognition and control of the sleep-wake cycle [13]. Thus, antihistamine might play dual function by targeting indirect pathway and upregulated histaminergic signaling in PD.

1.2 PROBLEM STATEMENT

Around 6.1 million people had diagnosed with PD in 2016, among which 47.5% were women and 52.5% were men & according to American Parkinson Disease Association (APDA), around 1 million people in the U.S. are having PD and more than 10 million individuals worldwide are suffering from PD. Still there is no cure available for PD but some drugs are there in the market to treat the symptoms & slow down the progression of disease.

Before the motor symptoms turn up, around 50-70% neurons in SNc are degenerated. In order to reduce the adverse effects, researchers can work on either of two approaches. Modification of currently used levodopa drugs with better efficacy and minimal side effects or to look for an alternative medication which would have good results on patients with least possible adverse effects.

Thus, the treatment with the ability to reinstate conventional basal ganglia functions might act as an analeptic intervention by reverting the motor symptoms that arise due to the adverse effects of current therapies used for PD. Also, traditional treatment neglects non-motor symptoms in PD as it is mainly implemented to improve motor dysfunction and therefore, novel pharmacological targets are required to treat both motor & non-motor signs and to enhance the current analeptic strategies used to treat PD.

1.3 OBJECTIVE OF STUDY

- To identify antagonists of dopamine D2-like receptors via drug repurposing approach.
- To screen approved antihistamine drugs as potential inhibitor of dopamine D2-like receptors.
- To compare the screening result and identify if repurposing approved drugs can be used instead of current medication.

CHAPTER – 2

LITERATURE REVIEW

2.1 PARKINSON'S DISEASE

Parkinson's Disease (PD) is a well-known, multifactorial [14], second most common neurodegenerative [15] and age-related disorder [16] with a high risk in the male gender [17]. It occurred due to the loss of dopamine-producing neurons in the region of the midbrain [18], [19], which leads to dopamine deficits and alteration in the basal ganglia circuit. The presence of Lewy bodies (α-synuclein aggregates) is the hallmark of PD [20]. Symptoms of PD are broadly classified into 2 types [21]: (i) Motor symptoms and (ii) Nonmotor symptoms that lead to functional damage to the body. Motor symptoms and signs include bradykinesia, postural instability, tremor, akinesia, rigidness with several other attributes like precision grip impairment, speech problems and gait disturbance, while the non-motor symptoms are comprised of several events including hyposmia, impaired colour vision, anxiety, depression, constipation, early cognitive dysfunction, dementia and sleep disorders which significantly accountable for the disability of patient and also escalate the risk of mortality [22]. It has been reported that the non-motor symptoms are developed before the emergence of motor signs of PD. Thus, they are also known as pre-motor symptoms [23]. They can also be used as biomarkers in the diagnosis of PD [24]. But the foremost thing is to identify the correct pathophysiology of the disease. In the pathophysiology of PD, studies revealed that the changes occur in the striatal dopamine receptors; for example, increased number of dopamine receptors are linked with dyskinesias, psychotic trauma, on-off phenomena, while the decreased number of dopamine receptors is associated with the disability of the patient and loss of response to levodopa [25]. To date, curation of PD is not possible, but some drugs are there in the market to treat the symptoms and slow down the progression of the disease. Among these drugs, levodopa has been considered as the most effective medication and gold therapy for PD as it can reverse disabilities and also improve quality of life by acting as a dopamine replacement agent. However, long-term administration of levodopa results in levodopa-induced dyskinesia (LID) [26], and a recent study [27] has reported that the

early onset of LID is related to the rapid dose increase of dopaminergic drug. This highlights the need for another effective drug to treat PD with the presence of minimal adverse effects. Besides dopamine, other neurotransmitters levels are also found

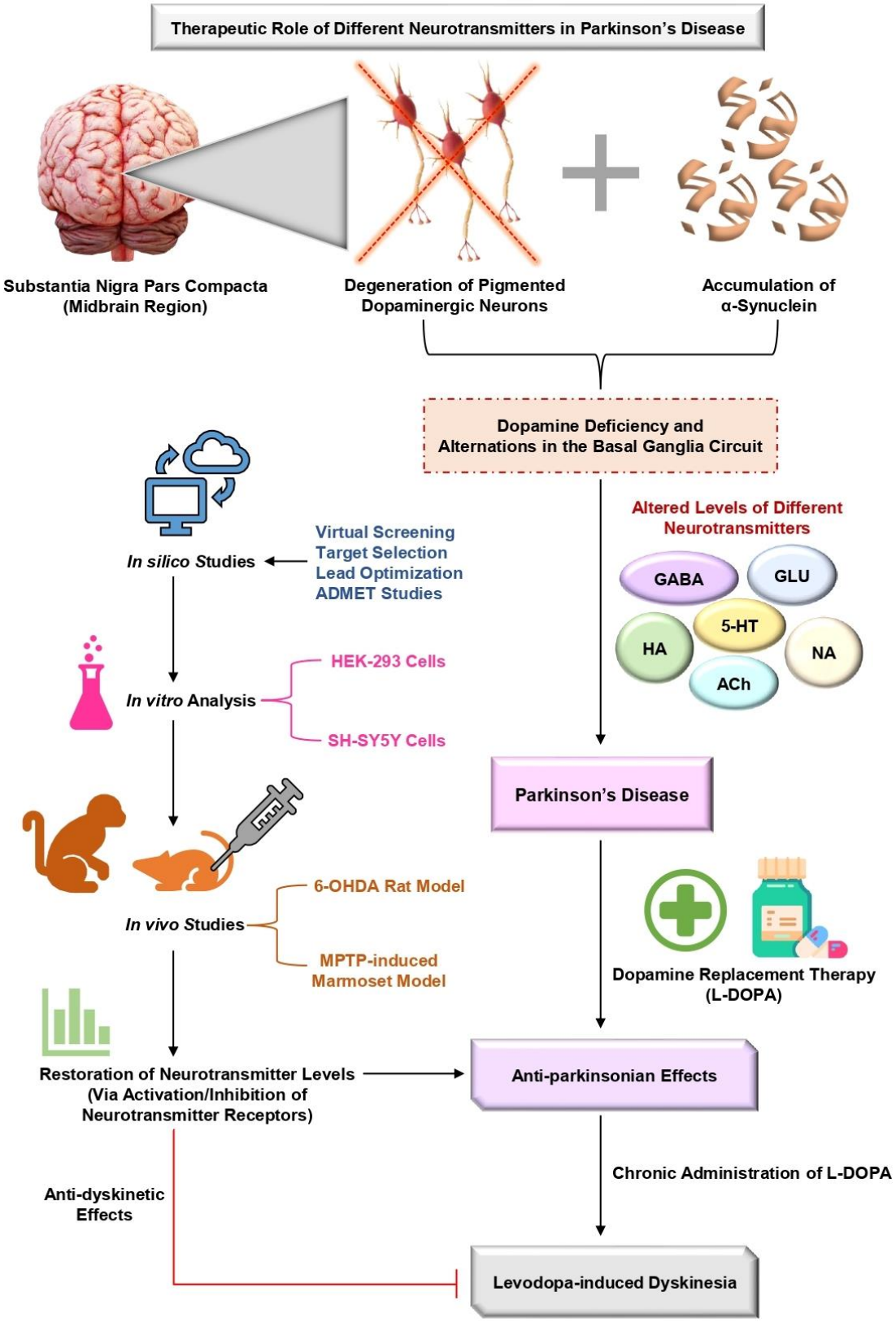


Figure 2.1: Role of different neurotransmitter receptors in Parkinson's Disease

to be altered; thus, these neurotransmitters, together with their different and distinct receptors, can be targeted against PD [3] (**Fig 2.1**). Altered striatal neurotransmitter levels have been observed in PD; for instance, levels of GABA and serotonin are found to be decreased while glutamate, acetylcholine and histamine levels are upregulated [28]. PD involves complex changes in several pathways, which include specific changes in the expression of neurotransmitter receptors [29]. Thus, these non-dopaminergic systems, including glutamatergic, serotonergic, GABAergic, histaminergic, adrenergic and cholinergic pathways within the cortex, brainstem and basal ganglia, are also very crucial for the therapeutic aspect [30]. Few drugs are already accessible in the public domain, and several drugs are currently under clinical trials, which are focused on the non-dopaminergic system. For example, pimavanserin acts on serotonin receptors, and it is used to treat non-motor symptoms like visual hallucinations and psychosis in PD [31], [32]. It has been observed that the non-dopaminergic system can target non-motor symptoms more efficiently as compared to the motor system of PD [33].

2.1.1 Symptoms and Diagnosis of PD

Symptoms are majorly of 2 types: (a) Motor symptoms & (b) Non motor symptoms, that leads to functional impairment. Motor symptoms and signs include bradykinesia, postural instability, tremor, akinesia, rigidness with several other features like precision grip impairment, micrographia, and speech problems and gait disturbance [34]. Non motor symptoms include hyposmia, impaired color vision, anxiety, depression, constipation, early cognitive dysfunction, dementia and sleep disorders which significantly responsible for disability of patient and even increase the risk of mortality [35], [36]. It is also suggested that non-motor symptoms may present even earlier then the emergence of motor signs of PD [37]. Thus, they can be serves as possible biomarker for the detection purpose with higher significance and greater reliability. And also, it will be cost effective method as compared to currently available methods.

Primary step in the diagnosis of PD is based on history and physical examination of the individual but majorly relies on the motor symptoms and initially it requires the presence of bradykinesia along with the minimal existence of any one of the features including: Muscle rigidness, or 4- to 6-Hz rest tremor, or postural fluctuations that are not due to the primary cerebellar, vestibular, visual or proprioceptive dysfunction [38]. Certain signs

and symptoms should not be present, for example neuroleptic therapy at emergence of symptoms, babinski signs, cerebellar signs, initial extreme dementia associated to disruption of memory, language and praxis, existence of a cerebral tumor or communicating hydrocephalus on CT scan report, oculogyric crises, history of repeated head injuries/strokes with stepwise development of parkinsonian features [39]. Due to lack of accuracy in other diagnostic method functional imaging is required for authentication of the clinical diagnostic method and to identify the underlying cause of the disease. Imaging technique for PD includes metabolic positron emission tomography (PET), dopaminergic PET/ SPECT diffusion-weighted MRI, hybrid PET–MRI, and amyloid-β PET [40]. Among in these imaging techniques discrimination of PD from atypical parkinsonism (which is a frequent diagnostic issue in the clinic) such as multiple system atrophy or the progressive supranuclear palsy can be done accurately by using structural/ diffusion-weighted MRI & metabolic PET while to look into dementia which commonly complicates the degree of PD, some useful and efficient tools are amyloid-β PET, metabolic PET, and cholinergic PET [41].

2.1.2 Current treatment of PD

Existing drugs used by PD patients majorly includes [42]:

a) Dopamine agonists,
b) MAO-B (Monoamine oxidase-B) inhibitors,
c) Levodopa (also called L-Dopa),
d) COMT (Catechol-O-methyl transferase) inhibitors, &
e) Some other drugs like anticholinergic drugs.

Among these drugs (**Table I**), levodopa has been considered as the most effective medication for PD as it could reverse the disabilities and also improves quality of life by acting as dopamine replacement agent [43]. Despite the effectiveness of levodopa, it also has several adverse effects which are associated with the emergence of erratic absorption & fluctuating plasma level and prolonged levodopa therapy results in chronic treatment complicacies for example levodopa-induced dyskinesia (LID) & motor fluctuations [44]. Recent modification for enhanced levodopa effect includes formulation for inhalation uptake through the lungs, gastric retentive formulations, and also levodopa prodrug associated to nutritional molecules, solubilized levodopa for continuous subcutaneous infusion, extended-release microspheres controlling drug release, all these products are

currently under development [44].

Table I: Existing drugs used to treat PD symptoms and associated adverse effects

Drug Class	Generic Name (Brand Name)	Adverse Effects	References
1. Levodopa	Carbidopa-levodopa (Sinemet) [Immediate-release drug]	Nausea, vomiting, postural hypotension, dyskinesias	[45]
	Carbidopa-levodopa (Parcopa) [Orally disintegrating drug]	Low blood pressure, nausea, confusion, dyskinesia	[46]
	Carbidopa-levodopa (Duopa) [Enteral suspension]	Headache, dizziness, nausea, difficulty in sleeping, vomiting	[47]
	Carbidopa-levodopa (Rytary) [Extended-release drug]	Dyskinesia, insomnia, headache, sweating, salivation	[48]
2. MAO-B Inhibitors	Selegiline (l-deprenyl, Eldepryl)	Hallucinations, cardiac related adverse effect, postural hypotension, nausea, dizziness, insomnia, confusion	[49]
	Safinamide (Xadago)	Nausea, dizziness, somnolence, headache, back pain, transient mild dyskinesia	[50]
	Rasagiline (Azilect®)	Hypertension, postural hypotension, headache, dizziness, nausea, vomiting, joint pain, hallucinations, sleeping issues, anxiety, rashes, impaired liver function, weight increases/decreases	[51]
3. Dopamine Agonists **(a) Ergoline class**	Bromocriptine (Parlodel, Cycloset)	Constipation, nausea, vomiting, asthenia, dizziness, headache, rhinitis	[52]
	Cabergoline (Caberlin, Dostinex, Cabaser)	Constipation, nausea, dizziness, headache, fatigue	[53]
	Pergolide (Permax)	Constipation, diarrhea, sedation, postural hypotension, nausea, dizziness, arrhythmia, dyspnea, hallucinations, confusion, psychosis, visual disorders	[54]
	Lisuride (Dopergin, Proclacam, Revanil)	Nausea, orthostatic hypotension, fatigue, dizziness, dyskinesia, headache, vertigo, peripheral edema, Mitchell's disease, sweating, dyspnea	[53]
(b) Non-ergoline class	Pramipexole (Mirapex)	Dyskinesia, postural hypotension, constipation, hallucinations, nausea, asthenia, sleeping issues, dizziness, extrapyramidal movement, headache, edema of lower extremities, confusion in mind	[55]
	Apomorphine hydrochloride (KYNMOBI™)	Reactions at the site of injection, contusion, discharge through nose, nausea, vomiting, confusion, dizziness, peripheral edema dyskinesia, somnolence,	[56]

		hallucinations	
	Rotigotine Transdermal System (Neupro®)	Dyskinesia, reaction at the site of application, postural hypotension, vomiting, headache, difficulty in sleep, drowsiness, tiredness, edema of lower extremities, diaphoresis, nausea, dizziness	[57]
	Ropinirole (Requip®)	Dyskinesia, excess sleepiness, edema of lower extremities, constipation, fatigue, vomiting, hypotension, dizziness, postural hypotension, nausea, impulse control disorders	[58]
	Piribedil (Clarium, Pronoran, Trastal, Trivastal)	Vomiting, dizziness, hypotension, postural hypotension, syncope, confusion, nausea, agitation	[59]
4. COMT Inhibitors	Opicapone (Ongentys®)	Dyskinesia, constipation, insomnia, urinary tract infection, dry mouth, dizziness, somnolence, weight loss, hallucinations, creatine phosphokinase level increases	[60]
	Entacapone (Comtan®)	Dyskinesia, diarrhea, nausea, urine discoloration	[61]
	Tolcapone (Tasmar®)	Dyskinesia, nausea, vomiting, anorexia, insomnia, orthostatic symptoms, hallucination, urine discoloration	[62]
5. Anticholinergic Drugs	Benztropine (Cogentin®)	Dry mouth, confusion, blurred vision, memory dysfunction, light headedness, orthostasis, dysuria	[63]
	Trihexyphenidyl HCL (formerly Artane®)	Dry mouth, constipation, dizziness, vertigo, headache, confusion, blurred vision, nausea, anxiety, nervousness	[64]
6. Adenosine antagonists	Istradefylline (NOURIANZ™)	Dyskinesia, nausea, constipation, hallucination, insomnia, somnolence	[65]
7. Others	Zonisamide	Decreased appetite, dyskinesia, nasopharyngitis, somnolence	[66]
	Amantadine	Difficulty in sleeping, dizziness and lightheadedness, hallucinations, dry mouth, nausea, orthostatic hypotension, constipation, peripheral oedema	[67]

2.2 Basal ganglia structure in the brain

The basal ganglia depict a multifarious circuit and its foremost function is to process sensory-motor information accurately [68]. The basal ganglia circuit is an imperative part of the management of behavior such as locomotion, reward learning, eye movement, etc., and elementary traits of the basal ganglia are conserved throughout vertebrate phylogeny [69]. In the basal ganglia functional organization, Striatum (Str) the major input nucleus of the circuit which collects projections from virtually all regions of cortex and then via

the input nuclei information passes to the two regions; MGP & SNr that stands for medial globus pallidus and substantia nigra pars reticulata, which are the output nuclei; then the information finally moves to ventrolateral thalamus which ultimately projects back to the cortex that results in closing of the loop [70]. Signals from Str to the output nuclei can be reach directly as well as indirectly, in case of direct pathway there is a monosynaptic link among the neurons that express the dopamine receptor, D1 and gamma amino butyric acid-ergic (GABAergic) neurons in region of SNr and the globus pallidus internus (Gpi) whereas in the case of indirect pathway which emerges from another group of neurons that express dopamine receptor, D2 that project to region of lateral globus pallidus (LGP) & then moves to Gpi from the region of subthalamic nucleus (STN) as a glutamatergic relay and LGP sends GABAergic projections to the STN which further send it to the MGP & SNr and also send it back to LGP; also, few scientists identified that LGP sends GABAergic projections to the MGP along with STN , schematic depiction of basal ganglia circuit is shown in **Fig. 1a**. The gradual loss of dopaminergic neurons in SNc region and the associated dopaminergic denervation of the Str lead to a cascade of complicated alternations in the regulation of basal ganglia nuclei as shown in **Fig. 1b**; in this process glutamate plays a vital role specifically at two regions of the circuit: Str and STN [71]. Functional re-organization of the basal ganglia circuit develops due to the neurodegeneration of neurons in PD [72]. This ensues in the augmented activity of output nuclei in the basal ganglia, which would be the consequence of intensified glutamatergic neurotransmission from the STN [73]. Studies suggest that in the expansion of PD, escalated activity of an indirect pathway is the foremost contributor [74]–[76].

2.3 ABERRANT NEUROTRANSMISSION IN PD

Targeting and modulation of various neurotransmitters may have the potential to terminate the dopamine deficiency. Dopamine is a catecholamine neurotransmitter, having several functions in the brain like cognition, locomotor activity, food ingestion, endocrine regulation, etc. [77], and the dopaminergic system has been studied with a lot of emphasis in the past five decades because of the association of dysregulation of dopaminergic neurotransmission (dopaminergic signaling cascade is illustrated in **Fig. 2.2**) with various diseases such as PD [78], Schizophrenia [79], Tourette's syndrome [80], thus agonist and antagonist of dopamine receptor play a key role in the treatment of these

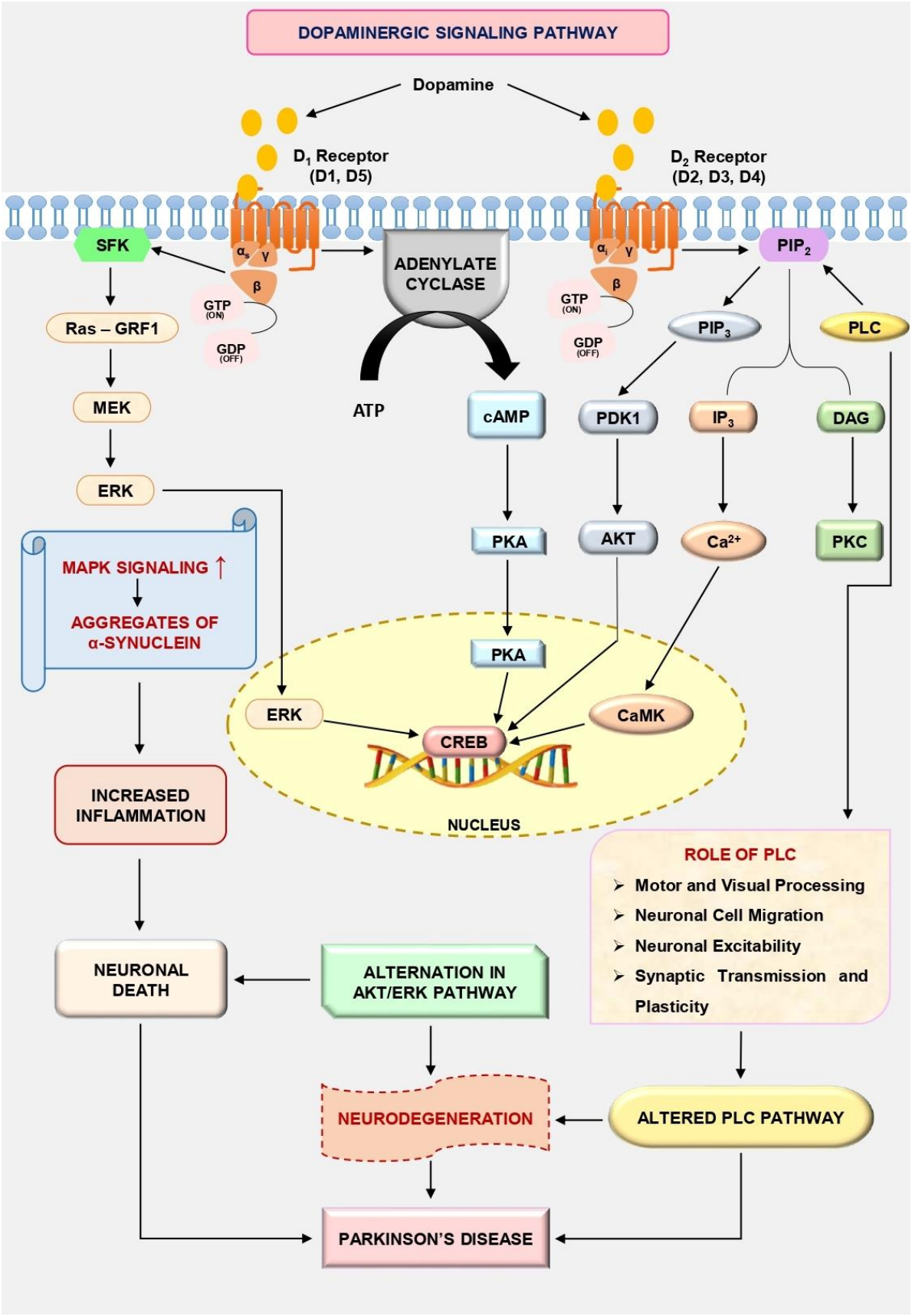


Figure 2.2: Depiction of dopaminergic signaling

diseases, for example, to increase hypokinesia in PD patients, agonists of dopamine receptors [81], [82] are used while antagonists have been developed for the blockade of hallucinations and delusions occurring in the patients of schizophrenia [83]. Degeneration of dopaminergic neurons in PD leads to upregulated glutamatergic neurotransmission, which ultimately contributes to motor dysfunction [84]. 19 distinct receptor binding sites of glutamate were analyzed in Pitx3ak mice mimicking PD condition, among which 11 out of them were found to be altered, including various GABAergic, cholinergic, dopaminergic and serotonin receptors [85]. In 6-OHDA mice, AMPAR levels remained unaffected while NMDAR expression was upregulated in the Str, causing overactivity of glutamatergic neurotransmission [86]. Upregulation of mGluR5 was observed in PD patients when compared with healthy individuals in the striatal region during PET/CT study [87]. Within the basal ganglia region, mGluRs are extensively expressed, and modulation of these receptors is able to regulate various functions such as neuronal excitability [88], [89]. In PD patients, overexpression of ERK-pathway is associated with dyskinesia which might further be associated with aberrant glutamatergic and dopaminergic signaling in the Str [90]. The serotonergic system is involved in various CNS diseases, including PD [91]. Serotonin is a monoamine neurotransmitter that regulates the function of several peripheral organs, and drugs that modulate serotonin receptors are extensively used in psychiatric and neurological disorders [92]. Serotonin is also known as 5-hydroxytryptamine (5-HT). Dysfunction of the 5-HT system performs a vital role in symptoms of PD, both motor and non-motor symptoms like LID, insomnia, depression, etc., and progressive and non-linear degeneration of serotonergic neurons has been observed in PD [93] confirmed by PET and other molecular imaging studies [94]. Central serotonergic function can be evaluated using loudness dependence of the auditory evoked potentials (LDAEP), so this can serve as a potential biomarker in early-onset PD patients to assess serotonergic neurotransmission [95]. It has been shown that altered GABA levels are present in the basal ganglia of PD patients, and these altered levels are associated with axial symptoms (specifically with the degree of gait disturbance); thus, it may be possible that the GABAergic neurotransmission has a significant role in the development of some axial symptoms of PD [96]. In a study including 60 PD patients using functional magnetic resonance imaging (fMRI), it has been observed that the severity of disease and levels of GABA can be correlated inversely in the motor cortex [97]. Alteration of GABAergic transmission has been found with chronic depletion

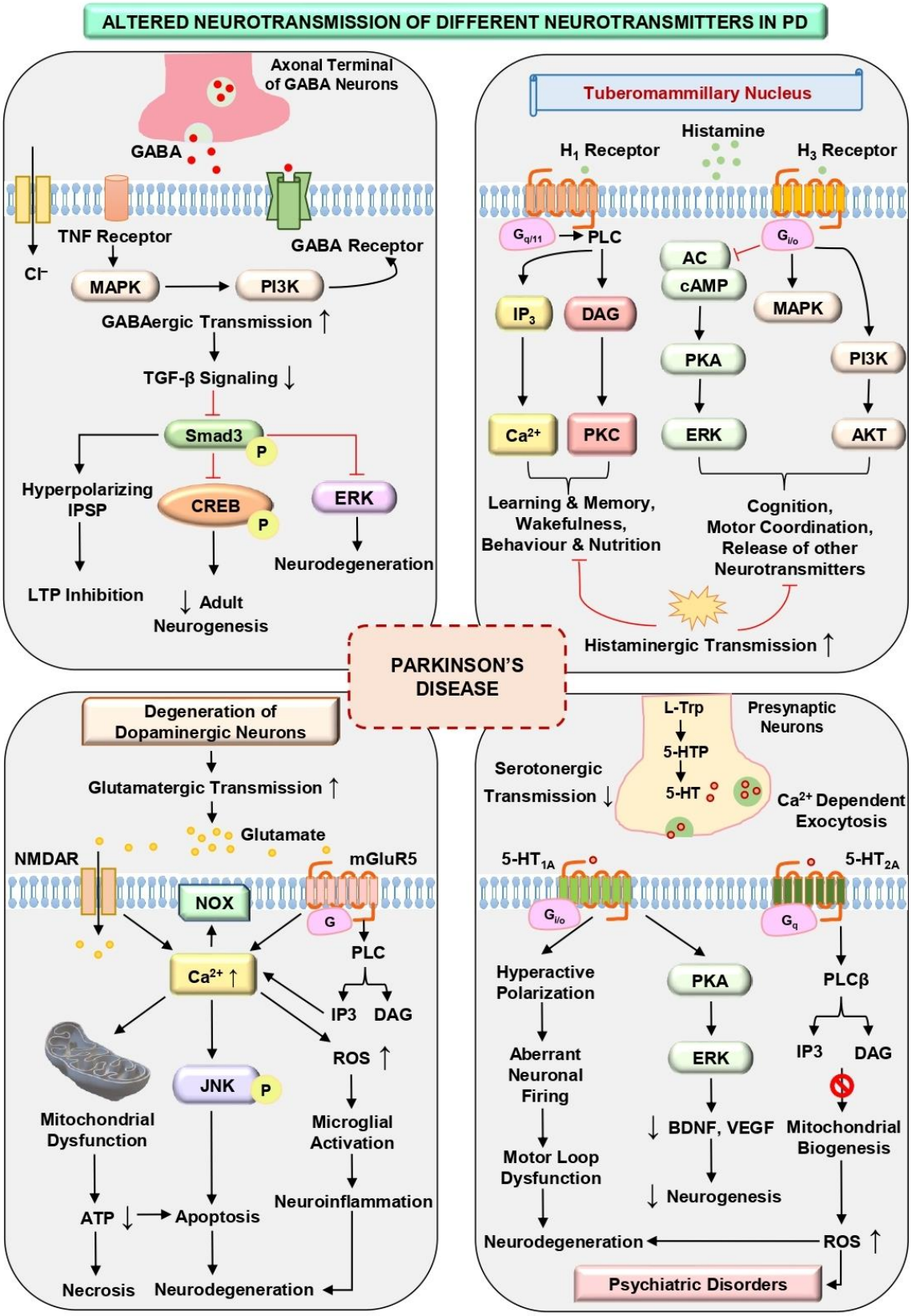


Figure 2.3: Aberrant neurotransmission contributing to the pathophysiology of PD

dopamine in the striatum [98]. Increased choline levels are found in PD [99]. Dopamine and cholinergic system have a perplex anatomical association, and the cholinergic interneurons (CINs) play a key role here in the regulation [100]. Studies suggested that in PDD, because of less Aβ load, cholinergic replacement therapies are efficacious when compared with other neurodegenerative dementias with high Aβ concentration [101]. In an SPECT study, scientists have found that disturbed limbic-paralimbic and prominence cholinergic networks are linked with PDD [102]. They are responsible for controlling locomotion and coordination [103] and can provide a potential therapeutic target against cognitive deficits and dementia in PD [104]. The noradrenergic system is structurally positioned at the nucleus of the brainstem called locus coeruleus [105], the prime source of synthesis of noradrenaline and noradrenergic projections virtually reaches all regions of the brain. The noradrenergic system performs a vital in regulating the synthesis of BDNF as astrocytes express several subtypes of adrenergic receptors [3] (mentioned in **Fig. 2.4**), which have the capability to get activated by noradrenaline & coupled with cAMP production and result in CREB activation via PI3K and MAPK pathway [106]. In rodents, substantial noradrenergic cortical depletion suggests a clear sign of coeruleo-cortical noradrenergic system degeneration, and in PD patients, 50% decline in cortical noradrenaline levels were reported [107]. In PD, increased histaminergic innervation is present at the superior colliculus of SN with altered morphology and release of HA has many effects, such as activation of microglia and astrocytes [11].

2.3.1 Implication of different neurotransmitter receptors in PD

As neurotransmitters play a fundamental role in the functioning of the brain, proteins and neurotransmitter receptors which are associated with the synthesis and activation/inactivation of neurotransmitters, are potent targets for therapeutic drug development with greater impact on the neurological disorder [108]. Neurotransmitters are also essential in controlling the endocrine system. Different types & sub-types of neurotransmitters are illustrated in (**Fig. 2.4**). Neurotransmitter receptors are not only limited to the dendrites; they are also found on the cell bodies as well as on presynaptic terminals. Different neurotransmitter receptors, along with their implications in PD, are summed up in (see **Fig. 2.3**).

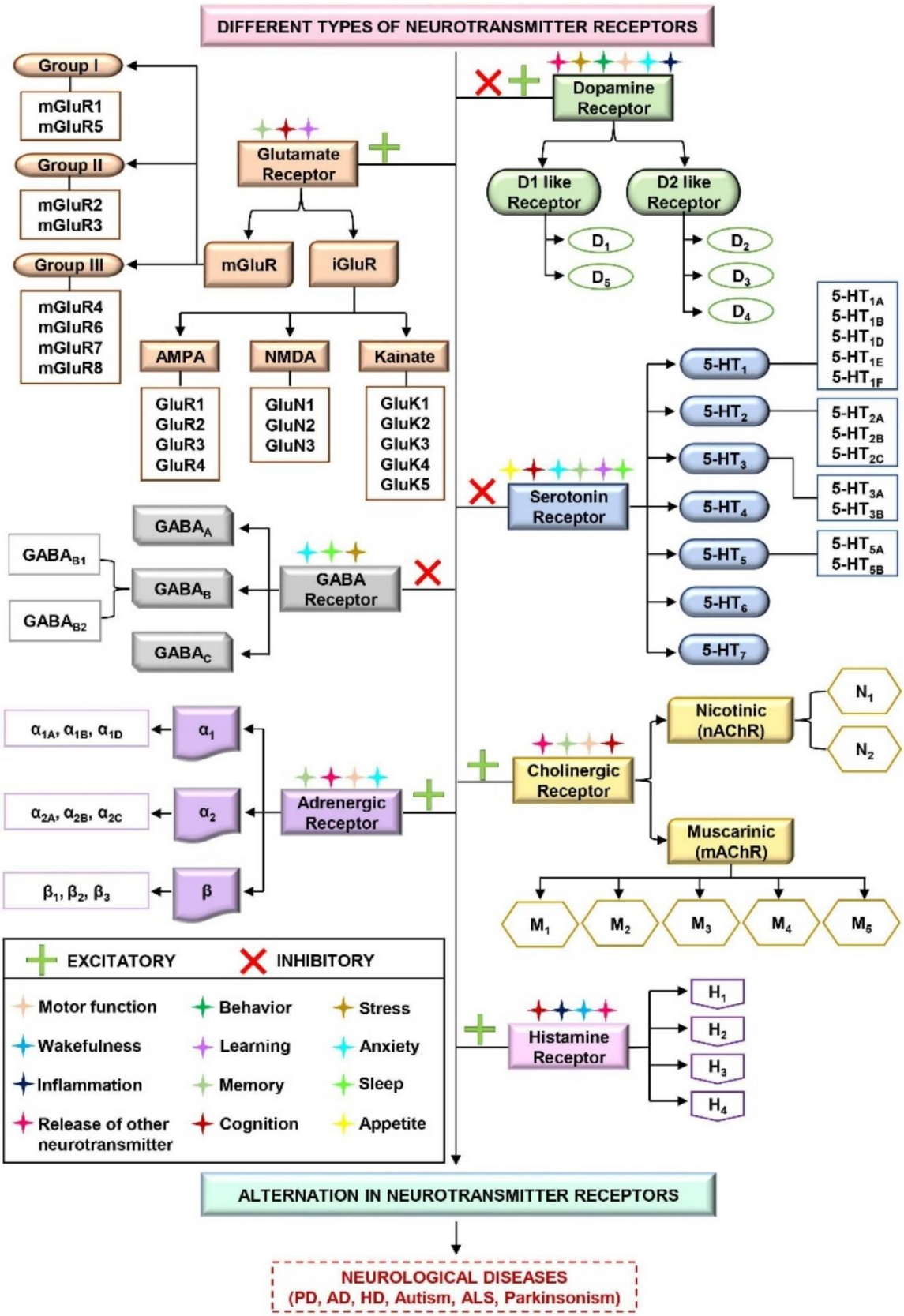


Figure 2.4: Different types of neurotransmitters associated with the pathophysiology of PD

2.3.2 Dopamine receptors

Dopamine receptors are mainly of two types [109]: D1 like dopamine receptors (D1, D5) and D2 like dopamine receptors (D2, D3, D4). Different properties of dopamine receptors are mentioned in (**Table II**) [3]. In neurons, activation of D1 receptor resulted in eEF2 dephosphorylation and this caused an upregulation of the Brain-derived neurotrophic factors (BDNF), and synapsin2b expression, which was accompanied by the least but remarkable elevation in the general protein synthesis and this translation pathway provides a therapeutic target for the treatment of depression and psychiatric disorders [110].

Table II: Types of dopamine receptors

Receptor Class	D1	D5	D2	D4	D5
Chromosome location	5q 35.1	4p 15.1-16.1	11q 22-23	3q 13.3	11p 15.5
Gene name	DRD1	DRD5	DRD2	DRD3	DRD5
Abundance in CNS	Most abundant	Less abundant	Second most abundant	Third most abundant	Least abundant
Localization in brain	Substantia nigra, hypothalamus, amygdala hippocampus, frontal cortex, striatum, caudate nucleus, olfactory tubercle	Substantia nigra, hypothalamus, pre frontal cortex, putamen, caudate nucleus, nucleus accumbens, amygdala	Hypothalamus, Putamen, Cerebral cortex, ventral tegmental area, olfactory bulb, striatum	Islands of Calleja, cortex, striatum, putamen, caudate nucleus, nucleus accumbens	Hypothalamus, amygdala, frontal cortex, nucleus accumbens
Isoforms	-	-	3	2	-
Mass (in KDa)	49.29	52.95	50.61	44.22	43.90
Polypeptide length	446	477	443	400	419
Amino acid in COOH terminal	113	116	16	16	18
Post-translational modification	Glycosylation, disulfide bond, lipidation	Glycosylation, disulfide bond, lipidation	Glycosylation, disulfide bond, lipidation, ubiquitination	Glycosylation, disulfide bond	Glycosylation, disulfide bond, lipidation, ubiquitination
Chemical binder	Cinnarizine, imipramine, mirtazapine, trimipramine	Cinnarizine, imipramine, mirtazapine, trimipramine	Amphetamine, desipramine, imipramine, maprotiline, mirtazapine	-	Chlorpromazine
Interactors (Small molecules)	Acepromazine, amoxapine, bromocriptine, cinnarizine, clozapine, ergotamine, iloperidone, imipramine, loxapine, methotrimeprazine, phenylpropanolamine, pipotiazine, pramipexole, propericiazine, quetiapine, ropinirole, rotigotine, thioproperazine, thioridazine, trimipramine, ziprasidone, ergoloid mesylate, dopamine, cabergoline, methylergometrine, olanzapine, apomorphine,	Apomorphine, aripiprazole, dopamine, zuclopenthixol, bromocriptine, chlorpromazine, cinnarizine, cabergoline, fenoldopam, olanzapine, carphenazine, levodopa, mirtazapine, ergotamine, imipramine, lisuride, methotrimeprazine, pergolide, pramipexole, quetiapine, ropinirole, rotigotine, trimipramine, ziprasidone	Olanzapine, aripiprazole, apomorphine, bromocriptine, cabergoline, chlorpromazine, haloperidol, pergolide, pimozide, flupentixol, levodopa, loxapine, metoclopramide, paliperidone pipotiazine, prochlorperazine, risperidone, thiothixene, acepromazine, clozapine, perphenazine, ropinirole, thioproperazine, trifluoperazine, ziprasidone, acetophenazine, buspirone, domperidone, fluspirilene, molindone, quetiapine, sertindole, thioridazine, alizapride, amantadine, carphenazine, chlorprothixene, droperidol,	Aripiprazole, bromocriptine, cariprazine, olanzapine, haloperidol, amisulpride, asenapine, cabergoline, chlorprothixene, levodopa, mirtazapine, pergolide, pramipexole, ropinirole, paliperidone, risperidone, sulpiride, ziprasidone, amoxapine, apomorphine, as-8112, captodiame, chlorpromazine, clozapine,	Apomorphine, ropinirole, clozapine, chlorpromazine, dopamine, iloperidone, lisuride, methotrimeprazine, pergolide, quetiapine, remoxipride, rotigotine, asenapine, flibanserin, levodopa, aripiprazole, cabergoline, olanzapine, paliperidone, pramipexole, promazine, propiomazine, risperidone thiethylperazine, ziprasidone, amoxapine, bromocriptine

	flupentixol, fluphenazine, carphenazine, chlorprothixene, fenoldopam, levodopa, lisuride, mirtazapine, pergolide, acetophenazine, aripiprazole, asenapine, chlorpromazine, haloperidol, minaprine, paliperidone, perphenazine, promazine, propiomazine, risperidone, thiethylperazine, thiothixene, trifluprom azine, zuclopenthixol,		fluphenazine, zuclopenthixol, amisulpride, asenapine, mesoridazine, methotrimeprazine, mirtazapine, pramipexole, remoxipride, sulpiride, thiethylperazine, amoxapine, bifeprunox, brexpiprazole, cariprazine, cinnarizine, dopamine, doxepin, ergoloid mesylate, ergotamine, iloperidone, itopride, ketamine, lisuride, minaprine, promazine, propiomazine, trifluprom azine, amphetamine, aniracetam, as-8112, bicifadine, brasofensine, bromopride, desipramine, imipramine, lurasidone, maprotiline, memantine, mianserin, nortriptyline, promethazine, rolicyclidine, rotigotine, trimipramine, yohimbine	domperidone, dopamine, iloperidone, lisuride, methotrimeprazine, pimozide, quetiapine, remoxipride, rotigotine, yohimbine	
Accession no. (UniprotKB)	P21728	P21918	P14416	P35462	P21917
Type	Stimulatory receptor (Gs-coupled)	Stimulatory receptor (Gs-coupled)	Inhibitory receptor (Gi-coupled)	Inhibitory receptor (Gi-coupled)	Inhibitory receptor (Gi-coupled)
Function	Memory, locomotion, renal control, impulse control, sleep	Vasodilatation, stimulation of renin secretion, cognition, attention, decision making, motor learning	Sleep, sexual activity, attention, memory & learning	Cognition, regulation of food ingestion, impulse control, sleep, attentiveness	Attention, cognition, sleep, sexual activity, impulse control
Mechanism	Via activating adenylyl cyclase activity	Via activating adenylyl cyclase activity	Via inhibiting of adenylyl cyclase activity	Via inhibiting of adenylyl cyclase activity	Via inhibiting of adenylyl cyclase activity
Signaling affected	PLC signaling, PKA and PKC pathways	PLC signaling, PKA and PKC pathways	PLC signaling, PKA, PKC pathways, β-arrestin pathway, EGFR, GIRK signaling pathway	PLC signaling, PKA, PKC pathways, β-arrestin pathway, EGFR, GIRK signaling pathway	PLC signaling, PKA, PKC pathways, β-arrestin pathway, EGFR, GIRK signaling pathway
Examples of associated neuronal diseases	PD, schizoaffective disorder, psychosis, TS, ALS, unipolar depression, schizophrenia	PD, schizoaffective disorder, psychosis depressive disorder, unipolar depression, schizophrenia,	PD, AD, HD, bipolar disorder, schizoaffective disorder, psychosis, TS, fibromyalgia, hyperprolactinemia, RLS, post-traumatic stress disorder, OCD, autism	PD, MDD, AD, HD, bipolar disorder, TS, schizoaffective disorder, psychosis, hyperprolactinemia, RLS, schizophrenia, DAN, delirium, acromegaly	PD, MDD, AD, HD bipolar disorder, schizoaffective disorder, psychosis, TS, RLS, treatment resistant depression hyperprolactinemia, schizophrenia, DAN

In a study, anxiolytic and antidepressant-like effects along with increased neural stem cell proliferation, neuronal differentiation and long-term persistence have been shown by agonists of D1 receptor in rats via positive regulation of a signaling pathway known as the Wnt/β-catenin pathway in the hippocampus [111]. Earlier, one study revealed that D2 receptor on astrocytes suppresses neuroinflammation, and now using the PD mouse model, it has been suggested that agonist of D2 receptor inhibits activation of Nod-like receptor protein 3 (NLRP3) inflammasome via a β-arrestin2-mediated mechanism, as NLRP plays a vital in the pathogenesis of PD thereby D2 receptor agonist might provide novel pharmacological relevance associated with PD [112]. It has been discovered that

D3 receptors also participate in the regulation of neuronal development and contribute to structural plasticity, along with the ability to trigger neuroprotective mechanisms via intracellular pathways [113]. Data has also proven that D3 receptors form active and functional heteromers by executing direct interaction with the other receptors and these heteromers have distinctive pharmacological properties like for instance, nicotinic acetylcholine receptors (nAChR) found on dopaminergic neurons form a heteromer with D3 receptors, which act as a molecular modulator of neurotrophic effects mediated via nicotine thus, it can provide pharmacological targets for PD [113].

2.3.3 Histamine receptors

Histamine receptors have been classified into four types: H1. H2, H3, and H4; are G protein-coupled receptors. Several studies indicate the negative impact of the histaminergic system on the progression of PD [114], as HA levels increase in PD shown in PD animal models, and this could be associated with an accelerated rate of degeneration of pigmented dopaminergic neurons in the SNc [115]. In PD, elevated HA levels might link with neovascularization [114]. Antagonists of HA receptors improves motor and other symptoms in PD condition, thereby highlighting its significance in the clinical response [116]. TNF-α upregulation has been found in several neurodegenerative diseases, including PD, AD and ALS [117]. It has been demonstrated that famotidine, an antagonist of H2, receptor improves motor functioning in primates PD model [118]. But oral administration of famotidine showed no anti-dyskinetic effects in a human study, including 43 PD patients [119], no adverse events were reported. While another study using a different antagonist had some contradictory results. Chronic administration of immepip, an agonist of H3R, results in reduced LIDs in a rodent model by blocking the release of two neurotransmitters (Glutamate and GABA) and preventing ERK1/2 phosphorylation [120]. In the pathophysiology of PD, activation of microglial cells plays a vital role [121], and its activity is modulated by H4R. An antagonist of H4R, JNJ7777120, blocks the mRNA expression of CD68, IL-1b and TNF-a; along with this, it has been shown that JNJ7777210 does not have a direct effect on dopaminergic neurons [122].

2.4 THERAPEUTIC EFFECT OF DOPAMINE AND HISTAMINE RECEPTORS IN PD.

A recent study [123], has shown that as compared to non-dyskinetic control mice, dyskinetic mice have a remarkably higher expression level of D5 receptors, upon injection of SCH- 23390 (antagonist of D1 like dopamine receptor), dyskinetic behavior is inhibited after levodopa administration while injection of SKF-83959 (a partial agonist of D5 receptor) has remarkable dyskinetic movements without levodopa indicating a significant role of D5 receptors towards the pathophysiology of PD and associated dyskinetic effects. Upon activation via an agonist, the D3 receptors increase dopamine levels and as well as reduces α-synuclein aggregation. Activated D3 receptors also enhance secretion of the brain-derived neurotrophic factors (BDNF), thus, increases oxidative stress, improves neuroinflammation, and in addition, age of onset can be predicted by a mutation in the D3 receptors [124]. Yang et al., found that in the striatum, the D1 plus D3 combined level is even better correlated than the D1 and D3 alone to the clinical manifestations of Lewy bodies disease patients [125].

HA is a key regulator of microglial phagocytosis and production of reactive oxygen species (ROS), which are involved in neuronal death of dopaminergic neurons in the SNc as shown in in vivo model, and by using H1 antihistamines, HA-induced microglia activation can be prevented along with increased neuronal survival [126]. Alone antagonists of H1 or H4 are not able to affect the production of TNF-α and IL-1β [127] while using both receptor antagonists together inhibit the HA-induced microglia activation and also blocks the liberation of TNF-α and IL-1β from the brain of rat. In the hemiparkinsonian rodent models of PD, ranitidine which is also an antagonist of the H2 receptor, suppresses LID via regulating the accumulation of Delta FosB protein and ERK pathway, simultaneously preserving the therapeutic effects of DOPA in easing akinesia [128]. Upregulation of H3R has been found in the post-mortem study of PD patients, thereby indicating the possible role of H3R in the treatment of PD, for example, administration of inverse agonist of H3R (BF 2649) or partial agonist of H4R (clobenpropit) with antihistamine monoclonal antibodies remarkably prevent accumulation of α-synuclein in the striatum [129]. H4R is recognized as a new potential target for various neurodegenerative diseases like PD, ALS, etc.[130]. In a recent study, increased expression of H4R mRNA have been observed in the post-mortem study of PD patients [131]. And this study also demonstrated that JNJ prevents the decrease in dopamine in the striatum region of PD rats and improves TH-positive fiber degeneration along with the reduction in Lewy bodies count [131].

CHAPTER – 3

MATERIAL AND METHODS

3.1 MATERIAL USED

Database used: Drugbank, PubMed, ChEMBL, Pubchem, UniProt, Protein Data Bank (PDB), BioGRID.

Software used: Clustal Omega, SwissDock, DockThor, Swiss PDB Viewer, SwissADME, Biovia Discovery Studio Visualizer.

3.2 WORKFLOW

Dopamine D2-like receptors were selected as the target molecules from the literature survey. The aim was to screen antihistamine drugs against dopamine D2-like receptors to repurpose an antagonist that might target the aberrant indirect dopaminergic and histaminergic signaling in PD. List of FDA approved antihistamine drugs were identified by Drugbank. Further, the BBB (Blood Brain Barrier) permeable drugs were selected as ligands for the study. Flowchart of protocol has been depicted in **Fig. 3.1**.

3.3 METHODS FOR PREDICTION OF POTENTIAL COMPOUNDS

3.3.1 Retrieval of Receptor Sequences for Similarity Analysis

For the sequence similarity analysis, sequences of dopamine receptors, DRD2 (P14416), DRD3 (P35462), DRD4 (P21917) and histamine receptors, HRH1 (P3567), HRH2 (P25021), HRH3 (Q9Y5N1), HRH4 (Q9H3N8) were obtained in fasta file format from UniProt database (https://www.uniprot.org/uniprot/) [132]. Multiple sequence alignment was performed with the help of a freely available tool, Clustal Omega [133].

3.3.2 Data Extraction

3-D structure of dopamine receptors, D2 receptor, D3 receptor, D4 receptor were extracted from PDB (https://www.rcsb.org/) [134]. A total of 58 FDA approved

antihistamine drugs were mined from Drugbank [135]. Structures of these drugs were collected from Pubchem. Quetiapine, Eticlopride and Clozapine structures were also extracted. These are well-known antagonists of different D2-like receptors identified with the help of BioGRID database (https://thebiogrid.org/). These 3 drugs were used as control drugs for the respective receptor. ChEMBL database was used to assess different properties of ligands like molecular weight, a clinical phase of drug, IC_{50} value, rotatable bonds, number of hydrogen bond donor/acceptor [136]. And out of these 46 drugs were selected for further molecular docking studies.

3.3.3 BBB Permeability Analysis

BBB permeability analysis were done using online BBB permeability predictor tool (https://www.cbligand.org/BBB/mainpage.php).

3.3.4 Molecular Docking

The molecular docking was carried out using SwissDock [137] and DockThor [138] web server to understand the receptor-ligand interaction. The steps mentioned below were performed further:

a. Preparation of the Target Receptors

The 3-D structures of dopamine receptor 2, 3 and 4 were extracted from RCBS PDB in .pdb file format. Then, this .pdb file was opened in Biovia Discovery Studio Visualizer. The structures were modified and redefined by deleting unwanted molecules of water and heteroatoms. Further, to compensate the loss the structures were opened in Swiss PDB Viewer for energy minimization. Finally, the modified files were saved in .pdb format.

b. Preparation of the Ligand Molecules

The 3-D structures of ligands were retrieved in .sdf file format. Then, this .sdf files were converted in .mol2 file format using Biovia Discovery Studio Visualizer.

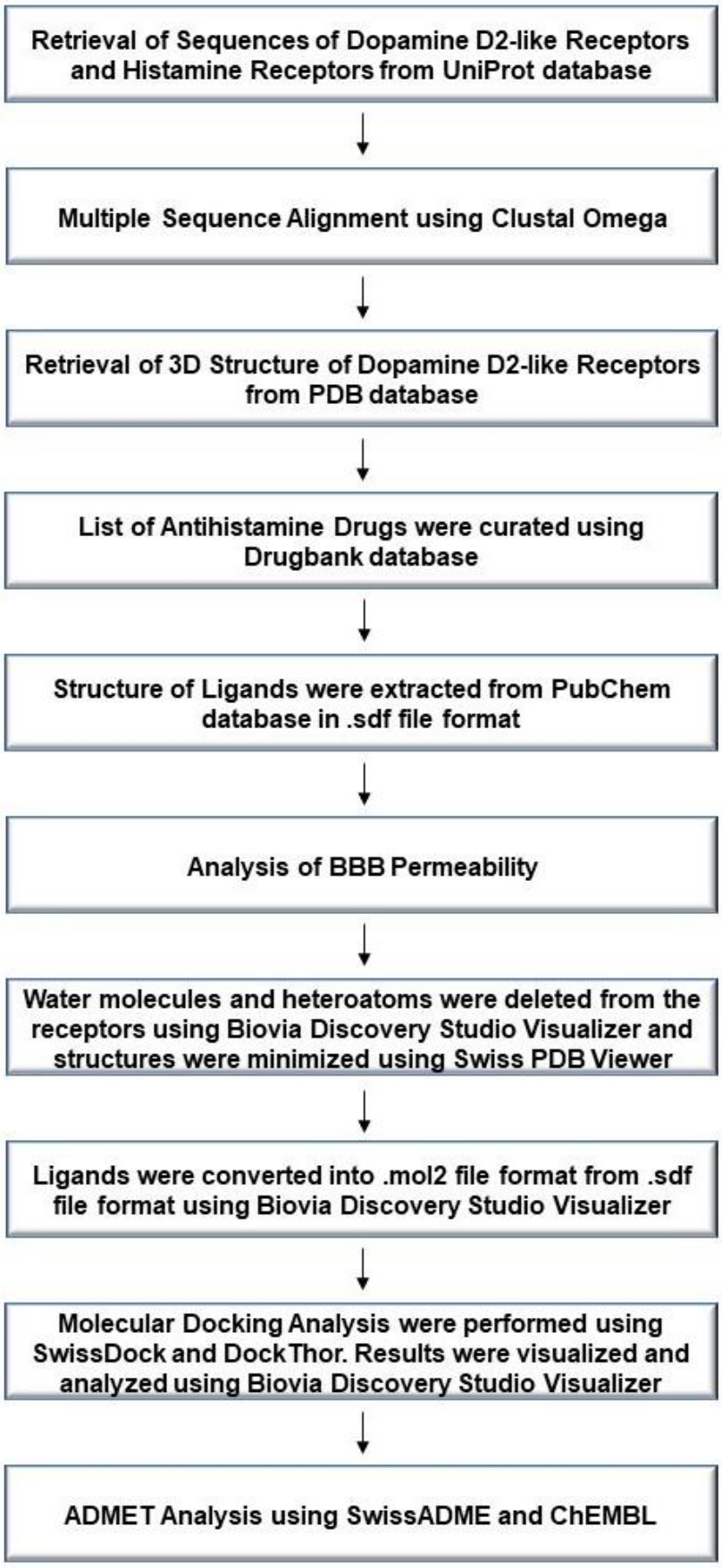


Figure 3.1: Flowchart of protocol followed

c. Molecular Docking Studies

After the successful preparation of the receptors and ligand structures, molecular docking analysis was performed by DockThor and SwissDock web servers. Interactions were visualized and evaluated with the help of Biovia Discovery Studio Visualizer.

3.3.5 ADMET Analysis

At last, ADMET analysis and pharmacokinetic properties were calculated using SwissADME and ChEMBL. It is a crucial step while identifying the lead molecules as it describes about the pharmacokinetics and drug-likeness of the compounds.

CHAPTER – 4

RESULT AND DISCUSSION

4.1 SEQUENCE SIMILARITY ANALYSIS

Sequence of dopamine (D2, D3, D4) and histamine receptors (H1, H2, H3, H4) were aligned. Similarities were present between dopamine and histamine receptor sequences. However, variations were observed in the length of the sequences. Regions of common amino acid were highlighted with black rectangles in the **Fig 4.1.** Different symbols indicate the match (*) and similarity with few mismatch (“:”), (“.”).

Different color indicates different type of amino acid. For instance, blue color represents negatively charged amino acid that are Glutamate (D) and Aspartate (E) while pink color represents positively charged amino acid including Arginine, Lysine and Histidine symbolized with one letter code, R, K, and H respectively. Polar and non-polar amino acid are represented with red and green colors respectively.

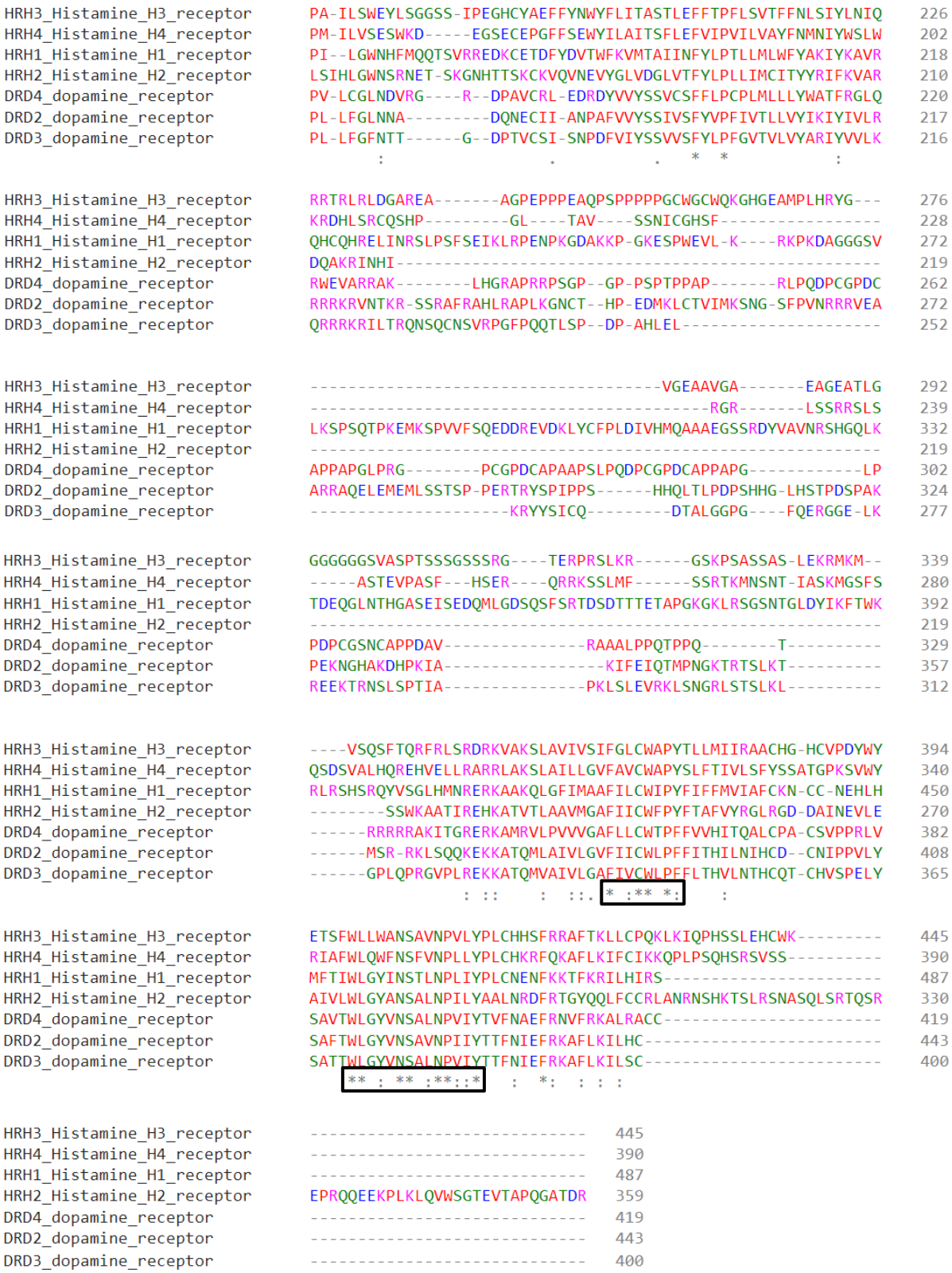
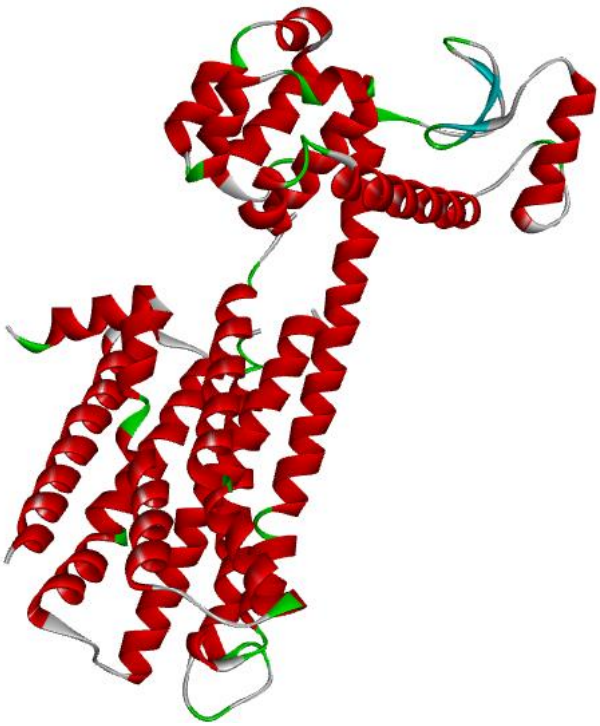


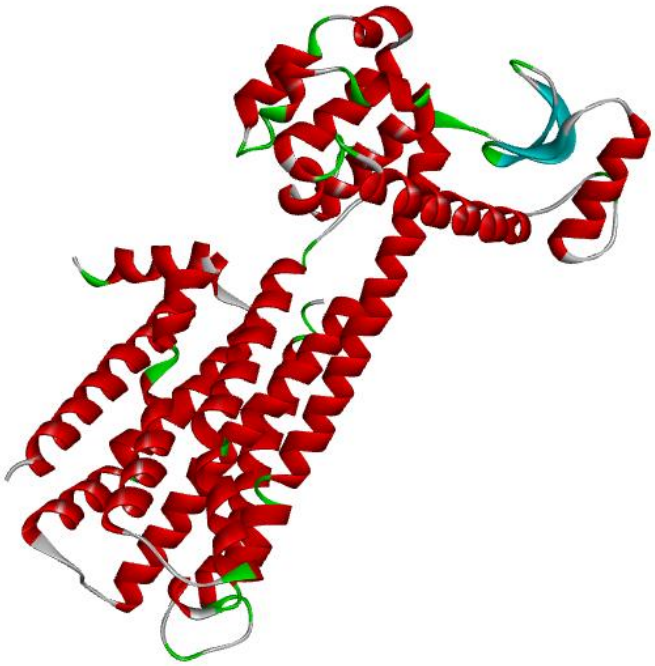
Figure 4.1: Dopamine D2-like receptor (D2, D3, and D4) sequences aligned with histamine receptors (H1, H2, H3 and H4).

4.2 STRUCTURES OF TARGET RECEPTORS

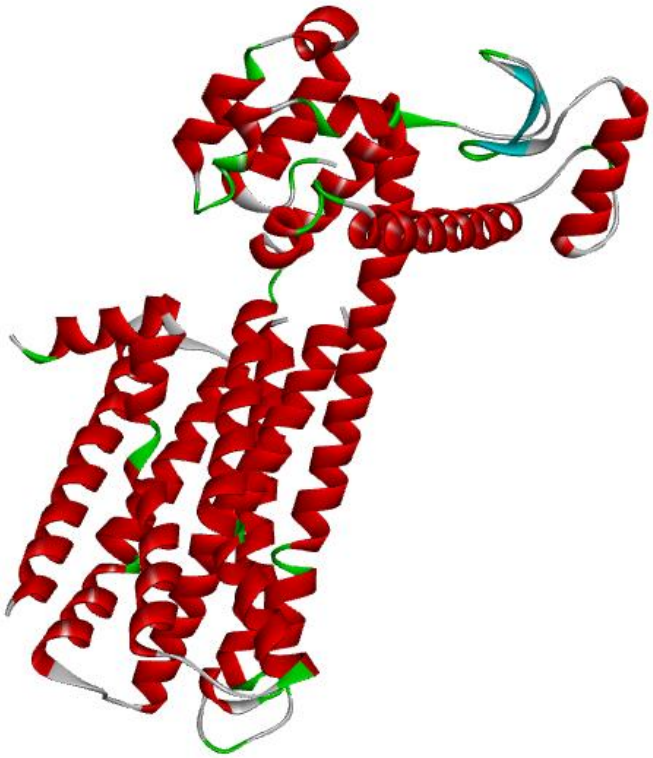
The energy minimized 3-D structures of dopamine receptors, D2, D3, D4 receptors were showed in **Fig. 4.2.**



(A) 3-D structure of dopamine 2 receptor



(B) 3-D structure of dopamine 3 receptor



(C) 3-D structure of dopamine 4 receptor

Figure 4.2: The 3-D structure of Dopamine D2-like receptors were obtained from PDB. (A) Dopamine 2 receptor, (B) Dopamine 3 receptor, (C) Dopamine 4 receptor. (Water molecules and heteroatoms were removed)

4.3 DOPAMINE D2-LIKE RECEPTORS ANTAGONISTS

With the help of BioGRID database, Quetiapine, Eticlopride and Clozapine were selected as the control drugs for D2, D3, and D4 receptor respectively. Each drug was docked with its respective receptor and docking scores were obtained. These values were used as cut-off scores against antihistamine drugs.

Table III: Binding energy of known Dopamine D2-like receptor antagonists

S.No.	Receptor Name	Drug Name	Estimated ΔG (kcal/mol)
1.	Dopamine receptor 2	Quetiapine	-8.4
2.	Dopamine receptor 3	Eticlopride	-8.22
3.	Dopamine receptor 4	Clozapine	-7.56

4.4 BBB PERMEABILITY ANALYSIS

The list of antihistamine drugs were mined from DrugBank database and their structures were obtained from PubChem. Further, these drugs were subjected to BBB permeability analysis. Out of 58 drugs, 9 were non-BBB permeable.

4.5 ANALYSIS OF RECEPTOR-LIGAND INTERACTION

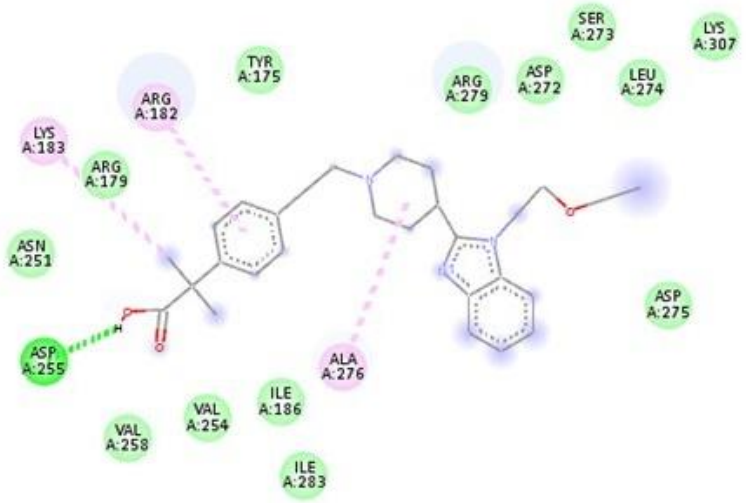
Out of 46 drugs, Bilastine was the only drug that met the required cutoff against all the three dopamine D2-like receptors. 7 compounds met the required cutoff of -7.56 kcal/mol in case of Dopamine D4 receptor whereas 5 compounds met the required cutoff of -8.22 kcal/mol in case of Dopamine D3 receptor. In addition, only 1 compound i.e., Bilastine met the required cutoff of -8.4 kcal/mol in case of Dopamine D2 receptor.

Table IV: Binding energy (in kcal/mol) of selected ligands

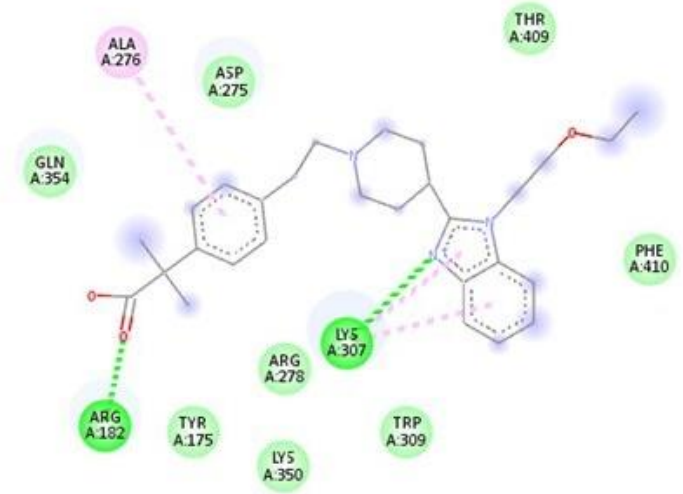
S. No.	Ligands	PubChem ID	D2 Receptor	D3 Receptor	D4 Receptor
1.	Bilastine	185460	**-8.84**	**-8.59**	**-8.7**
2.	Acrivastine	5284514	-8.33	**-8.48**	**-8.73**
3.	Hydroxyzine	3658	-8.15	-7.99	**-8.08**
4.	Buclizine	6729	-8.29	**-8.27**	**-8.44**
5.	Azelastine	2267	-8.13	-8.02	**-8.09**
6.	Cinnarizine	1547484	-7.89	**-8.44**	**-7.96**
7.	Olopatadine	5281071	-7.83	**-8.71**	**-8.13**

Bilastine was approved in 2007 and it is used for the treatment of urticaria and allergic rhinoconjunctivitis. It is characterized as a highly potent and specific inhibitor of histamine H1 receptor [139].

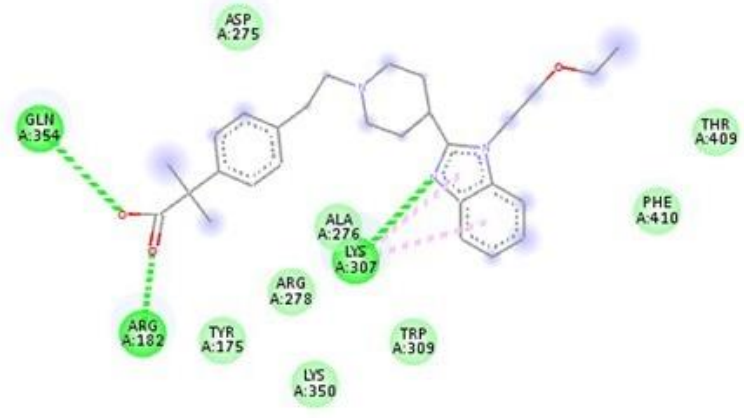
After analyzing the results, we observed that bilastine interacts with the Aspartate-255 residue of dopamine D2 receptor, Arginine-182 and Lysine-307 residues of dopamine D3 receptor via H-bond interaction. Similarily, bilastine interacts with the Arginine-182, Lysine-307 and Glutamine-354 residues of dopamine D4 receptor as shown in **Fig 4.3.** Van der waal and alkyl-alkyl interactions were also observed.



(a) Bilastine interaction with D2 receptor



(b) Bilastine interaction with D3 receptor



(c) Bilastine interaction with D4 receptor

Figure 4.3: Interaction between bilastine and Dopamine D2-like receptors

4.6 DRUG-LIKENESS OF THE SELECTED LIGANDS

The ADMET analysis and pharmacokinetic study are extremely imperative phases in the process of drug discovery and development. It was carried out with help of ChEMBL and SwissADME.

Table V: Physiochemical properties of selected ligands

Properties	Drug Name						
	Bilastine	**Acrivastine**	**Hydroxyzine**	**Buclizine**	**Azelastine**	**Cinnarizine**	**Olopatadine**
Molecular weight (g/mol)	463.62	348.44	374.90	433.03	381.90	368.51	337.41
H-bond donors	1	1	1	0	0	0	1
H-bond acceptors	5	4	4	2	3	2	4
Molar refractivity	140.53	109.18	113.12	140.20	115.27	125.86	99.23
Topological polar surface area (Å²)	67.59	53.43	35.94	6.48	38.13	6.48	49.77
Lipinski's rule of five	✓	✓	✓	✓ one violation	✓ one violation	✓ one violation	✓
Log P	4.03	3.43	3.94	5.01	3.85	4.32	2.97
Gastro Intestinal absorption	High	High	High	Low	High	High	High
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55	0.55
BBB permeant	Yes	Yes	Yes	No	Yes	Yes	Yes
Solubility	Poorly soluble	Moderately soluble	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble	Moderately soluble

Selection of drug must be done after estimating both the short-term benefits and long-term consequences. Another factor while selecting the drug is to consider patient-specific factors, for example level of disability, functional & chronologic age, drug tolerance and expected efficacy [140].

CHAPTER – 5

CONCLUSION AND FUTURE PERSPECTIVE

Current drugs used for the treatment of PD have several adverse effects to overcome these side effects alternate medication is required. The goal is to achieve a drug or combination of drugs that could have maximum efficacy with minimal adverse effects. Aberrant indirect pathway signaling mediated via dopamine D2-like receptors and upregulated histaminergic signaling have been observed as a major contributor in the pathophysiology of PD. Thus, antihistamine drugs might show therapeutic effects against this aberrant signaling cascade.

The docking of the ligands was carefully performed and their interactions were observed. From this study, it can be considered that Bilastine, an inhibitor of histamine H1 receptor possess high binding affinity for dopamine D2-like receptors. Thus, the information gained on the basis of docking score postulates a piece of preliminary evidence for its potential as a dopamine D2-like receptors inhibitor and anti-parkinsonian medication. It may be implemented in designing effective therapeutics for PD in the future.

In addition, structures similar to bilastine might show similar results. Thus, they can also be screened against dopamine D2-like receptors. Moreover, the selected compounds can be checked by exploration in cell culture assay. Also, the effect of compounds can be studied by cell viability and LDH assay. These experiments will adjunct the above data pertaining to the therapeutic competence of these chosen compounds to be used for PD.

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LIST OF PUBLICATION

1. D. Yadav and P. Kumar, “Parkinson’s Disease: An Overview and Role of Glutamate and its Receptors: Glutamate receptor based therapy as an alternate way to treat Parkinson’s,” in *2021 5th International Conference on Information Systems and Computer Networks (ISCON)*, Oct. 2021, pp. 1–5, doi: 10.1109/ISCON52037.2021.9702338.
2. Yadav D, Kumar P. Restoration and targeting of aberrant neurotransmitters in Parkinson's disease therapeutics. Neurochem Int. 2022 Mar 21;156:105327. doi: 10.1016/j.neuint.2022.105327. Epub ahead of print. PMID: 35331828.

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Respected Sir/Madam,

I, **Divya Yadav**, final year student of **M.Sc. Biotechnology**, Roll no. **2K20/MSCBIO/06**, Department of Biotechnology, Delhi Technological University, hereby declare that the work which is presented in the Dissertation thesis entitled "**In silico analysis of antihistamine drugs as neuroprotectants targeting dopamine D2-like receptors in Parkinson's Disease**" in the fulfilment of the requirement for the award of Degree of Masters of Science in Biotechnology is an authentic record of my own work done under the supervision of **Prof. Pravir Kumar**.

The work attached to this declaration complies with the University's requirements and is my own work. The overall similarity is 55%, out of which 51% is from my own publications. The plagiarism report has been attached. Further, the work attached to this declaration has not been submitted in full or partial satisfaction of an academic award in another university.

Yours sincerely,

Divya Yadav
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