THINK INDIA JOURNAL ISSN: 0971-1260

Vol-22-Issue-17-September-2019

Computer Aided Drug Discovery Against Parkinson Disease

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Abstract

Computer – aided drug discovery is an advanced technique being used in biotechnology for saving the time and money being used during lead discovery. It provides a promising solution to the problem. Different approaches like simulation, docking, etc. are being collectively used in this field. Parkinson disorder is worldwide age-related disorder having various severe symptoms. Traditional medicines include some precursor of dopamine which needs to be administered at regular intervals, but show different adverse effects. An advanced approach is to inhibit some of the enzymes which catalyses the degradation of dopamine, which is already present in lower amount in the brain. There are several genes and proteins such as LRRK2, UCHL1, etc. whose mutation and alteration have an association with the Parkinson disease. They prove to be potential targets against which drugs could be designed using CADD approach.

1. Introduction

The brain is main processing centre of a living organism. The proper functioning of the brain is very important for the survival and well-being of the organism. The brain along with spinal cord work together to form Central nervous system which controls all the vital functions of the body. It includes speech, thought, vision, body movements, etc.

The brain comprises of different types of cell, each having their exclusive characteristics. In the brain, the most prevalent cells are neurons and glia (non-neuron). Both types of cells are important for the proper brain function. Neurons are the building blocks and also, transmit information to different neurons, cells of other organs, tissues, etc. through chemical and electrical signals. Glia participates in the brain signalling and important for healthy functioning of neurons. **[1]**

Any pathological condition which affects the neurons and leads to loss of its structure and function is called as neuro-degeneration. There are several neuro-degenerative diseases which affects different neuron set in specific functional system. The main reasons for the cause and progression is not so well-established. But many diseases show some relation of genetic and environmental factors to their initiation.

There are a few hundred neuro-degenerative diseases currently estimated, several of those are related to each other. During progression also, they show different symptoms which makes it difficult to properly classify and recognize them. Due to the fact that such diseases affect the neurons, they affect the normal function of whole body. A simple loss in neural signal leads to severe risk in many organ systems. One of the major limitations in treatment of these diseases is the late diagnosis, because they progress very slowly and shows very less detectable symptoms**. [2]**

The neuro-degenerative diseases which are most common are Alzheimer, Huntington, Parkinson, and Amyotrophic lateral sclerosis. Increasing age is the most important risk factor in case of such diseases, specially Alzheimer and Parkinson disease.

In 1817, following Alzheimer's disease (AD), James Parkinson identified the key medical characteristics of the second leading neurodegenerative age-related disorder.After almost a span of 120 years, it was found that the loss of neurons in the substantia-nigra-pars-compacta (SNpc) is the central pathological feature of the Parkinson's disease (PD). In, 1958, Arvid Carlsson's discovered the role of dopamine in brain**. [3]** The nigro-striatal dopaminergic pathway was then identified to be developed from SNpc neurons. The depletion of SNpc neurons results in a lack of striatal DA, that is responsible for all the typical symptoms of PD.

The identification and development of novel drugs is a lengthy, complicated, expensive and potentially risky phase. At the preliminary level, in-vivo and in-vitro studies are not very beneficial. For this purpose, computer-aided drug discovery (CADD) techniques are commonly used to accelerate the process. The monetary advantage of drug development using analytical methods of lead discovery and lead optimization is important. **[4]** It is beneficial to use hit-to-lead optimization algorithms to cover multiple molecular range while limiting the number of molecules in vitro to be manufactured and evaluated.CADD's key objective is to develop formulations which binds strongly with the target showing higher free energy reduction, improved ADMET features, and is unique to the receptor.

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2. Parkinson disease

Parkinson disease is the 2nd most prevalent chronic idiopathic neurological disease behind Alzheimer disease. Tremor, bradykinesia and muscle stiffness along with poor gait and stance are described. Moreover, approximately half of patients having PDshowfronto-striatal-facilitated cognitive disorder, including concentration deficiencies, rate of information processing, linguistic disruptions, loss in learning and memory and impulsive behavior. **[5]** The signature symptom for PD is dopaminergic synaptic deficiency in (SNpc) substantia-nigra-pars-compacta or dopamine deficiency in the brain.

Although it is not well known the underlying mechanism for dopaminergic neuronal failure in SNpc. The onset and progression of PD may involve mitochondrial impairment, loss in energy, oxidative-stress, excite-toxicity, improper folding and accumulation of protein, deterioration of protein degradation mechanisms, and processes involving cell autonomy. The misfolding of proteins and their consequent accumulation in intracellular spaces between them has become a driving principle.**[6]** The primary protein which is improperly foldedand found in SNpc neurons extracellular gaps during PD are Lewy bodies, that comprise many misfolded and aggregated amyloid-protein, particularly alpha-synuclein, phosphorylated-tau and amyloid-beta-protein.

2.1 History and statistics

The first definition of PD signs and therapies were provided in the "Indian Ayurveda" and Chinese medical book "Nei-Jing" around 1500 BC to 500 BC. In 1817, it was accurately described by a British surgeon, James Parkinson on whom this condition was known as "the trembling paralysis." Research have shown, PD is common and impacts 1-2% of people over the age of 65 and 4-5% of people over the age of 85. **[7]**

PD appears to be more prevalent in males (approximately 1.5 times) than females and a greater proportion of PD had been identified in industrialized nations as a result of an increase in the aging population. **[8]** Ageing process has been the most predominant causal factor for PD. There are other possible causes, which include ecological toxin exposure.

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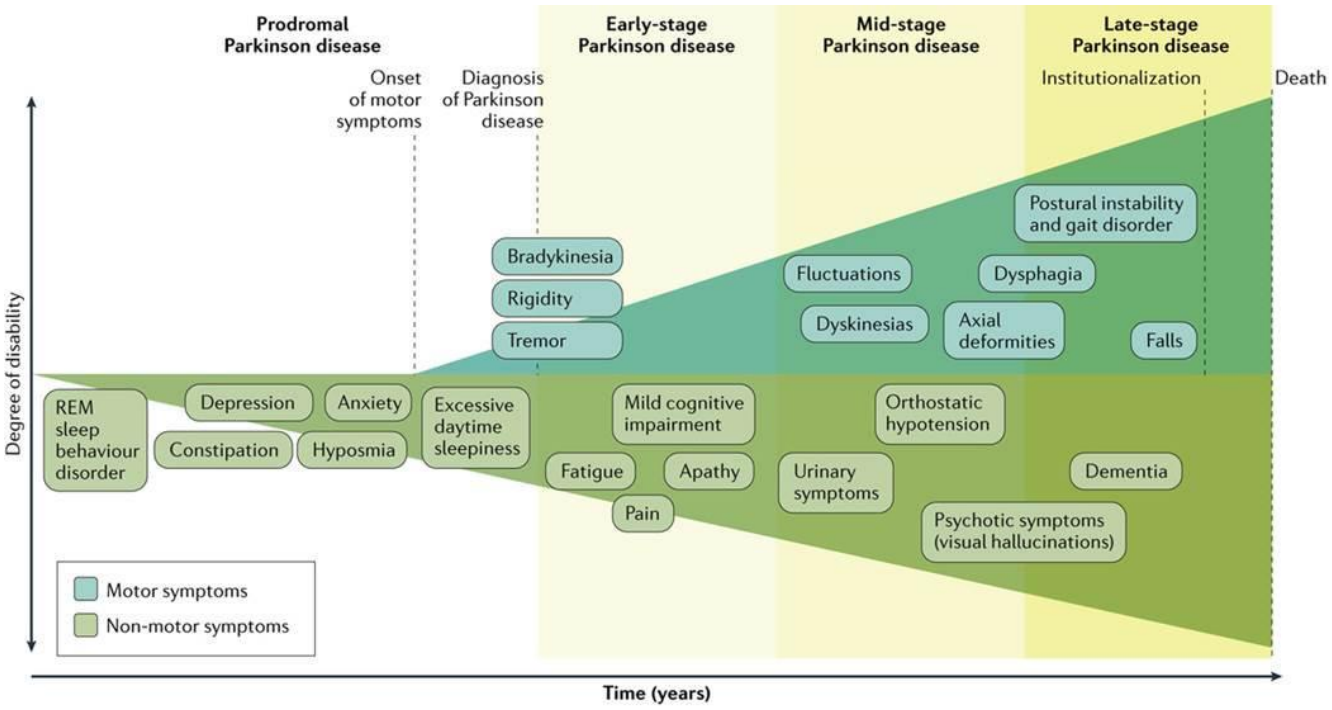
Many researchers, however, believe that PD is not a deadly disease on its own, but that it allows ordinary activity to deteriorate over age. However, a PD patient's average lifespan is typically same as healthy individuals.



2.2 Symptoms

Figure 1: Clinical symptoms associated with Parkinson disease progression [9]

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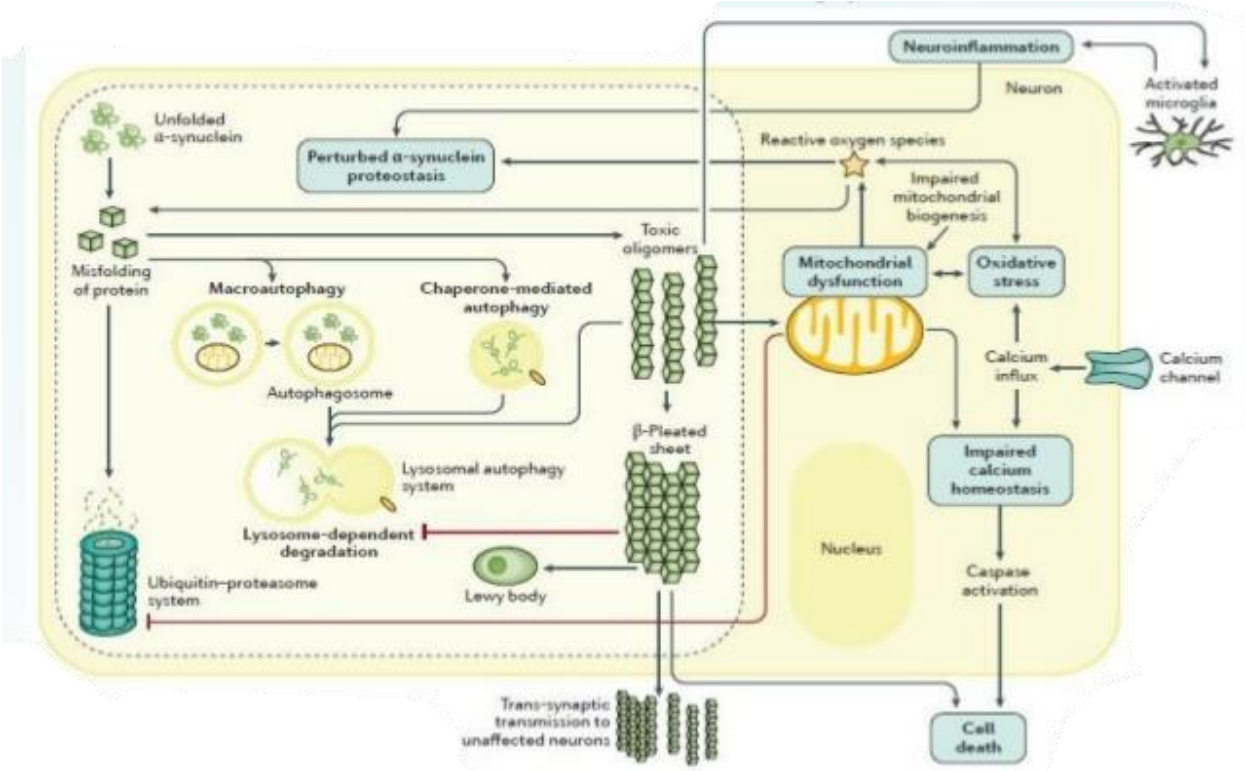

2.3 Mechanism

Figure 2: Molecular mechanisms involved in Parkinson disease. [9]

PD is a multifactorial disorder involving both evolutionary and non-genetic causes such as ecological factors. The most prominent underlying mechanisms in PD progression have included aggregation of misfolded protein components, protein removal mechanisms breakdown, mitochondrial disruption, oxidative stress, excite toxicity, cellular senescence, and genetic abnormalities. **[10]** There are several other reasons which have an influence in development of Parkinson's disease and its symptoms. During drug discovery, any of the gene, protein, enzyme or pathway can be targeted, so that inhibiting or promoting them could produce desired therapeutic response.

3. Drug discovery

Drugs are the tiny biological or chemical compounds that impair their operation or composition when introduced in a living system and are used to cure, alleviate, manage or avoid a disorder or to relieve pain. The process of identifying new potential medications is

the exploration of drugs. This covers a broad range of research, from medicine, biotechnology and combinatorial chemistry.

Earlier, most drugs were discovered by detecting the disease treating ingredient from traditional medications or by serendipitous discovery. Nowadays, with advancement in technology and research, the mechanism of disease is being studied at molecular, genetic and physiological level and the specific genes and proteins are being targeted.

3.1 Drug discovery process

The first step in the drug discovery process is the characterisation of the disease process and identification of drug therapeutic targets. They are some protein or messenger RNA which, when modified by a drug, favourably affects the outcome of a disease. Then, the molecules which interacts and induce some therapeutic effect on the targets are identified. These molecules are called ligands and they are further screened for different properties such as interaction energy, toxicity, etc.

After the discovery process is completed, a few potential drugs are proposed and they are further studied in drug development phase. A very lengthy, complicated, costly and potentially risky phase is the exploration and development of a new drug. For average, the arrival of a drug into the market requires 10-15 years and US$ 500-800 million. **[11]**

3.2 Computer-aided drug discovery

In initial phases, (CADD)computeraided drug discovery techniqueis broadly utilised to speed up the drug discovery process and keep costs low. In the lead optimization stage of drug research, the cost benefit of using machine learning tools is significant. A large portion of the total sum is invested in production and lead analogues testing. Applying computational methods in the hit-to-lead optimization process is therefore helpful. This helps to reduce the number of molecules to be synthesized and evaluated in vitro and an enormous amount of money.

The computational tools are used for optimizing the hit compound involving:

- Structural assessment of molecular docking and energy parameters of target analogues,

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- ligand-based testing of molecules with similar chemical form or enhanced biological efficacy
- Predicting and controlling medication metabolism and pharmacokinetics in favour of preference
- Absorption, distribution metabolism, excretion and toxicity (ADMET) properties.

The core goal of CADD is to model molecules that are strongly attached to the target, showing a substantial reduction in free energy, improved ADMET features and unique fortarget. In comparison to chemical synthesis and physiological analysis of molecules, the comparativereduced cost helps to reduce the uncertainty of time and space and encourages the scientific community to proceed. **[12]**

3.3 Receptor theory

The CADD is generally based on the receptor theory, which is derived from several other theories. In 19th century, Paul Ehrlich provided the theory that medicinal factors perform their specific response to improve the symptoms of disorder by functioning as quick fixes at specific molecular sites in the system as a significant part of the classic theory of "lock and key". **[13]**This hypothesis has identified drugs as the ligands of receptors or substrates of enzymes that selectively calibrate function of unknown molecular receptors to cause therapeutic effects. Also considered is the conventional kinetic enzyme system on the basis of law of mass action derived from Michaelis and Menten in 1913. **[14]**

The receptor and ligand interaction could be defined as:

Receptor [R] + Ligand [L] $\longrightarrow$ [RL] $\longrightarrow$ R + Cellular Effect

The ligand is aligned with the receptor and alters the interaction dynamics between the receptor and its relevant membrane elements for modification of the cell and eventually the tissue's function.The property of prediction and communication with the receptor is called affinity, while efficacy is the ability of the ligand to affect biological process improvement by activating intracellular transduction pathways that included G-protein or ion channel complexes.

The ancillary ligand attribute is the specificity feature, which refers to the extent, the ligand integrates to the target having preference relative to similar structural objectives. The extent of specificity primarily assesses a new compound's symptom profile, provided when amplified further than the optimal range. The intended process alone has no negative effects.

Ligands can either be antagonists or agonists:

- Agonists seem to have inherent potency and their receptor binding results in stimulation of the cellular structures participating in cell or tissue neurobiological or medicinal response.
- Antagonists adhere to the target and inhibit the agonist's interaction when alone showing no influence on the cell. **[15]** Competitive antagonism is typically correlated with small molecules that specifically interfere with the attaching agonist receptor. The semi-competitive and pseudo-competitive antagonists associate at places apart from the agonist receptor and therefore can modify agonist interaction.

3.4 Molecular modelling

Molecular modelling is concerned with using a computer system to analyze, explain or evaluate some element of the characteristics of a molecule's architecture. **[16]** The molecular modelling methodologies typically involve auto framework generation, repository research, protein template building, diversity assessment, ligand docking or paradox mechanisms. Thereby, molecular modelling nowadays is perceived to be an area of research co-related to using different approaches to design and infer atomic level data from a model. At the other side, this field involves several computational chemistry approaches such as biochemical cycle energy estimation, energy minimization, etc. Computational chemistry has been perceived to be the essence in molecular modelling.

The recognition of bio-molecular entities participating in association to a particular receptor enables specific interpretation of the biochemical pathway necessary for its fundamental biological function. It is obvious that the reaction between a drug and the cellular target creates a physiological response. **[17]** The process of molecular identification controls this specific attachment and its scale. This process of cellular detection is designed in molecular simulation to consider the interaction of the drug-receptor.

3.5 Classification of CADD

CADD is commonly categorized into two groups:

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- Structure-based– CADD on the basis of structure is usually recommended wherein the target protein's high-resolution structural information is available. The central purpose of this system was essentially to produce substances that are strongly attached to the target, i.e. showing a greater decrease in free energy, improved DMPK / ADMET features and specific to the target.**[18]**
- Ligand-based– This uses all the information regarding recognized active and also inactive entities by looking for chemical resemblance and constructing predictive, statistical relationship structure-activity (QSAR) models. When there is no or little structural data available, it is preferred, often for targets of membrane proteins.

Based on availability of the structure of receptor and ligand, some other approaches of CADD are also used for the drug discovery and development.

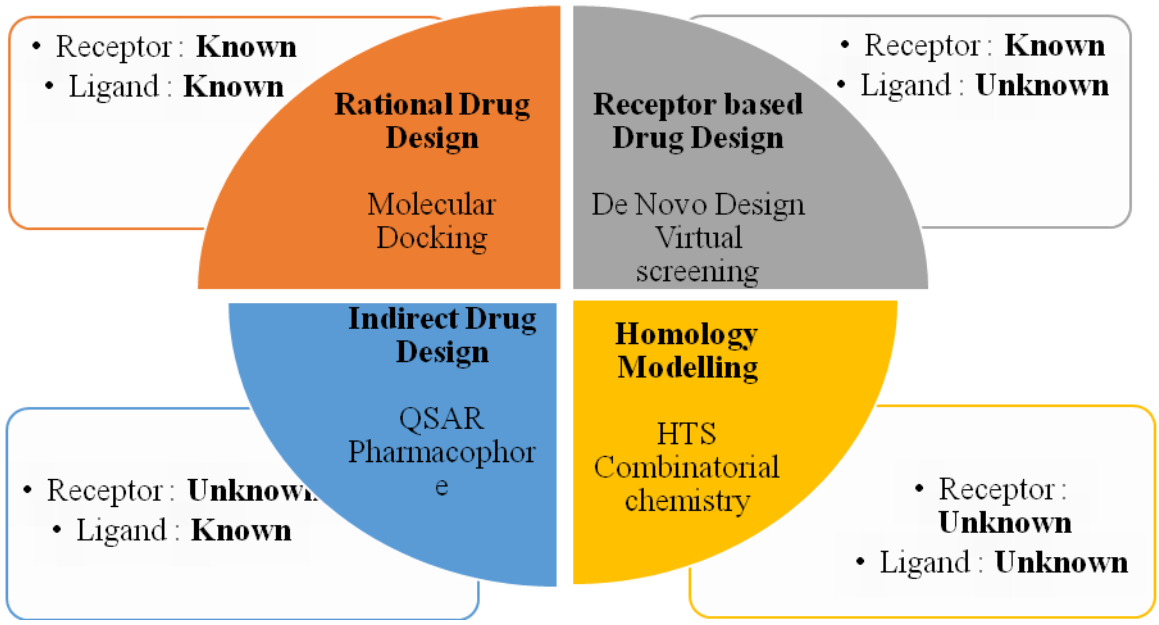

Fig 3: Different approaches of computer–aided drug discovery

4. Potential targets

The genes, proteins or enzymes which have a role in the Parkinson disease, and alteration in their structure or function might bring a therapeutic response may be proposed as potential targets. They generally consist of proteins and enzymes, which are functioning improperly due to any mutation in the responsible gene. So, inhibiting their function might help in controlling the disease and lead to treatment.

4.1 PARK 7

It provides instructions to make a protein DJ-1. Across different organs and tissues, including the brain, this protein is found. It helps in protection of brain cells from oxidative stress. It also serves as a chaperone molecule which helps in proper folding of newly synthesized protein and denatured protein. When some proteins are completely denatured, it delivers them to proteasomes for breaking down. **[19]**

Several mutations in this PD-associated gene. Most of these contribute to small and misfolded DJ-1 proteins which is abnormal or a switch in amino acids resulting in unstable or dysfunctional protein. Some mutation inhibits the production of this protein. Some mutation inhibits its chaperone activity. In case of Parkinson disease, neurons get lost in high number, and during oxidative stress, DJ-1 can no longer protect them resulting in huge loss of neurons.

4.2 Ubiquitin C-terminal hydrolase L1

This is mostly present in brain neurons. It is associated with proteasomes whichdegrades unwanted or damaged protein. In cells, such proteins are tagged with specific molecule called ubiquitin. It serves as a signal for the degradation. This system functions as quality control system of cells. Ubiquitin C-terminal hydrolase L1 (UCHL1) removes and recycles ubiquitin molecules from degraded proteins.

There are two mutation associated with Parkinson disease. A common polymorphism reduces the risk of disease. In the enzyme, serine is replaced by tyrosine at position 18. This may help in protection against Parkinson disease. Another change increases the risk of PD. In this, at position of 93, isoleucine is substituted by methionine, leading to decreased activity of hydrolase, disrupting the degradation mechanism. Damaged and misfolded proteins build up to toxic levels and damage neurons. This results in uncontrolled movements due to improper signalling.

4.3 Leucine rich repeat kinase 2(LRRK2)

It provides instruction to make a protein called dardarin. Such proteins, having leucine rich regions participate in interaction for signal transmission. It also has an enzyme activity. It helps in transferring phosphate group from ATP to amino acids. It also has GTPase activity.

There are many mutations associated to Parkinson disease. Most of them replace any single amino acid in dardarin protein, affecting its structure and function. It leads to problems in body movement and balance.

4.4 Cytochrome P450 2D6 (CYP2D6)

There are several chemicals which mimics MPTP, which are metabolic conversion products. These chemicals are generated from the smoking and drinking. Such chemicals act as neurotoxin that induce PD or enhance the progression. Cytochrome P450 2D6 is the enzyme responsible for the conversion of MPTP and other such chemicals to the toxic MPP+. **[20]**

Various studies suggest that inhibition of this enzyme might help in stopping this conversion and thus, controls the degradation of neurons.

4.5 Alpha-synuclein (SNCA)

Together with other related proteins, misfolded SNCA aggregates accumulate in SNpc DA neurons. They are called Lewy bodies and are characteristic pathology of PD. SNCA gene mutations trigger the early onset of familial PD, accelerated progression, and high dementia connection. **[21]** In animal and cell culture models, over-expression of it revealed aggregation of SNCAin mitochondria, significant defects in mitochondrial movement, and reduced mitochondrial membrane capacity.

4.6 Gluco-cerebrosidase (GBA)

GBA is believed to be one of Parkinsonism's most prevalent genetic risk factors. The mutations in it are linked with shifts in lipid levels, contributing to lysosomal processing disorder that can lead to synucleinopathies, as well as autophagy-lysosomal dysfunction. **[19]**GM1 synthase mutation or ganglioside-3 synthase (GD3S) upregulation is correlated with reductions in neuroprotective ganglioside (GM1) and rises in toxic gangliosides (GD3 and GT3 series) that may cause SNpc neurodegeneration.

4.7 Monoamine oxidase B (MAOB)

Monoamine oxidases A and B are external mitochondrial membrane enzymes that facilitate the oxidation to the corresponding imines of primary secondary and tertiary amines, including several neurotransmitters.The two enzymes share 70% amino acid identity. MAO A metabolizes serotonin, norepinephrine, and dopamine, while MAO B oxidizes benzylamine, creatine, and phenylethylamine ideally, and only gradually metabolizes

norepinephrine and serotonin. **[22]** MAO B also produces 1-methyl-4-phenyl-pyridinium, a direct causal factor of the condition of Parkinson, from 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP). Monoamine oxidase inhibitors are continuously being studied and clinically used to treat depression, and also Parkinson, Alzheimer, and many other neurodegenerative diseases.

4.8 Catechol-O-methyl transferase (COMT)

The inactivation of catecholamine neurotransmitters such as serotonin, epinephrine and norepinephrine require catechol-O-methyl transferase. The enzyme adds and inactivates a methyl group into the catecholamine.Levodopa, a precursor of catecholamine and a common drug used in case of PD is easily inactivated by COMT. COMT blockers prevent COMT enzyme activity. The application of a COMT antagonist delays the degradation of levodopa in the system, rendering it more available to the brain, thus enhancing its effectiveness. **[23]**

5. In-silico approach

It refers to mimicking the human body environment, protein structure, chemical structure in the computer system to understand the mechanism, interaction and modification. It involves various software and web servers which are designed by various institutes and organization working on biological data and bioinformatics.

5.1 Selection of receptor

Receptor refers to any protein or enzyme molecule which have an important role in the mechanism of disease and its interaction with some molecule either promoter or inhibitor, will surely produce some therapeutic response. They are identified by studying the literature and understanding the mechanism.

After the receptor selection is done, molecular structure of the receptor is fetched from database. 3-D structure of the proteins was fetched and downloaded from the Protein Data Bank database (https://www.rcsb.org/). It is a repository of the atomic coordinates, 3-d structure and other information of the proteins. All the submitted data are from experimental data after proper validation. **[24]**

If structure is not available in PDB, it can be predicted with the help of its sequence using homology modelling. It is usually performed on a web server, SWISS-MODEL (https://swissmodel.expasy.org). **[25]**

5.2 Optimization and validation of receptor

The receptor structure which is selected must be optimized by performing energy minimization and refinement. Energy minimization refers to selecting most stable structure or configuration on the basis of minimum energy by performing simulation.

For the purpose of refinement of protein structure, a protein structure refinement server 3D-refine (http://sysbio.rnet.missouri.edu/3Drefine) is used. It takes the PDB structure of the protein to get refined as its input. And, after performing energy minimization and folding arrangements, the results are given. This contains new refined structure along with refinement and RMSD scores to compare both the structures. **[26]**

5.3 Selection of ligand

Ligand refers to any chemical moieties that interacts with the receptor and this interaction produces some desired response. For ligand selection, several approaches are used.

For discovery of novel drug for the particular disease, the entire collection of drug molecules from a particular database such as ZINC, DrugBank, etc. are fetched and docked to see their interactions. For the virtual screening, an automated web server Pharmit (pharmit.csb.pitt.edu) is used. It helps in searching small molecules based on their chemical and structural resemblance to other entities which binds to the target protein. It follows the principle of pharmacophore building. After the process, it provides the results as small molecules with best interaction score and minimum RMSD value. These small molecules are downloaded from the respective server and serves as ligands for the drug discovery process. **[27]**

5.4 Validation of ligand

Ligands are validated on the basis of several parameters such as ADMET properties, QSAR analysis, Lipinski rule of fives, etc. There are some parameters which suggest that these ligands will bind to the target efficiently after getting properly absorbed and distributed in the body. Based on these, ligands are screened and the molecules which follow all the parameters are put forward as potential drug molecules.

SwissADME (http://www.swissadme.ch/) is a web server manged by Swiss institute of Bioinformatics. It helps in computing the physicochemical descriptors and also prediction of ADME properties, pharmacokinetic properties, drug-like nature and other properties. It takes

molecule structure in .mol format, or SMILES format as input. It calculates all the properties and provides all the information on a single page. **[28]**

pkCSM (http://biosig.unimelb.edu.au/pkcsm/) is a web server to predict pharmacokinetic properties including parameters of toxicity. Apart from the parameters describing absorption, distribution, metabolism, excretion, it calculates different values and parameters describing the toxic nature of the ligand. It contains AMES toxicity, hepatotoxicity, and others. **[29]**

5.5 Docking

Interaction of ligand and receptor is required to be studied for CADD. This is achieved by performing docking. It refers to binding of ligand to the active site of receptor in all possible configuration and then calculation of different parameters such as docking energy, atomic contact energy, inhibition constant, RMSD score, etc.

A web server, DINC (Docking INCrementally) (http://dinc.kavrakilab.org/) uses an incremental algorithm for exploration of the search space of potential binding sites of protein and ligand. It uses AutoDock Vina for the docking purpose. After docking, it gives the result in form of best three conformation having minimum energies, thus maximum binding score. It provides the 3D structure of those conformations for further study. **[30]**

Various software is used for this such as AutoDock Vina, PatchDock, etc. They provide result of the docked structure based on several parameters. On the basis of these results, few ligands (2-5) are selected and they are further analysed and modified.

5.6 Visualization

For the visualization of the protein structure, ligand structure and other interaction, a software package, PyMol is used. It is installed in the system and helps in visualization, interpretation and representation of the structure.

5.7 Drug candidates

Based on all these results, few molecules are declared as drug candidate. They exhibit therapeutic activity with optimum ADME properties, reduced toxicity and improved activity as compared to existing drugs, if available.

5.8 Drug development

After the drug candidates are selected, in-silico work is finished. The work is carried out further in the labs by performing in-vitro and in-vivo studies. During drug development, several pre-clinical and clinical trials are performed in different phases. All the progress along-with the limitations are recorded and filed for the drug approval from the government.

6. Conclusion

In spite of all the research work done in the field of Parkinson disease, there are several areas which are still untouched. This review provides an insight into all the basics of computer-aided drug discovery and some of the major mechanisms involved in PD. Looking at the advantages and possibilities of drug discovery using in-silico approach, it is a great field yet to be explored. There are several proteins and enzymes which have a role in the mechanism of the PD. Such molecules are expected to be potential targets. Some drugs are available in the market inhibiting some of the enzymes, but they have some major side-effects. The objectives of future research should be the optimization of targets, drugs to show no or minimum toxicity, which will ensure the advancement in the in-silico drug discovery process.

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