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MOLECULAR-LEVEL COMPARATIVE ANALYSIS ON HUB-PROTEINS OF PARKINSON'S DISEASE WITH SELECTED SYNTHETIC DRUGS USING AN *IN-SILICO* APPROACH

S. I. Aruna [*1], S. Sujatha [2], E. R. Chinchu [3] and E. S. Neenu [4]

Department of Biotechnology [1], Malankara Catholic College, Mariagiri, Affiliated to Manonmaniam Sundarnar University, Tirunelveli - 627012, Tamil Nadu, India.
Department of Biotechnology [2], Malankara Catholic College, Mariagiri - 629153, Tamil Nadu, India.
University of Kerala [3], Kariavattom Campus, Thiruvananthapuram - 695581, Kerala, India.
Indriyam Biologics Pvt. Ltd [4], Trivandrum - 695012, Kerala, India.

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Correspondence to Author:
S. I. Aruna

Research Scholar,
Department of Biotechnology,
Malankara Catholic College,
Mariagiri, Affiliated to Manonmaniam Sundarnar University, Tirunelveli - 627012, Tamil Nadu, India.

E-mail: arushabio@gmail.com

ABSTRACT: Physical interactions between proteins are cardinal to biological processes. To restore their function, proteins must interact with one another. Hub proteins are densely interconnected proteins with a wide range of biological significance and are also to blame for several illnesses, including cancer, autoimmune disorders, and neurodegenerative diseases. The most prevalent of these is Parkinson's disease. SNCA, alpha synucelin is a hub protein that is the main cause of this disease; along with this DJ 1 and Parkin also responsible for Parkinson's disease. Through this study, we performed a molecular-level comparative analysis on hub-proteins of Parkinson's disease with selected synthetic drugs using the *in-silico* approach. The binding energy and complex energy identified the better efficacy of the drug. The Lipinski rule of filtering and the ADMET pharmacological parameters were satisfied by seven out of the twelve medicines. Levodopa, among these medications, had superior effectiveness with 4RKW and 5C32 in both approaches. Better Lib Dock scores, binding energies, and complex energies with 4RKW were displayed by safinamide. The molecular dynamic modelling further validated the binding stability of the 4RKW-safinamide complex. The amount of GC content was also analyzed with the aid of a Python programme to establish the stability of DJ1.

INTRODUCTION: A network is made up of multiple nodes and is connected by edges. These nodes are called hubs [1]. For example, in a protein-protein interaction the proteins act as nodes and the interactions are edges. A scale-free network contains a small number of highly connected nodes. The connectivity is directly proportional to the number of proteins it interacts with [2]. The main advantage of this is the domain repeats which are associated with binding are associated with binding are enriched in hubs [3].

On the basis of the expression profile, the hubs are categorized into two groups: party hub and date hubs. The party hubs interact with most partners at the same time. Party hubs are the central or static part. They are long disordered regions compared to date hubs; indicating that the regions are important for flexible binding. They act as a core of highly clustered functional modules.

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But the date hubs are dynamic and they are unable to interact with most partners at same time [4]. Hub proteins have much importance in each and every field. Hubs are particularly interesting drug targets, they show importance in cancer research, and they show special biological properties more essential than non-hub proteins. Hub proteins show a fundamental role in modular organization of protein interaction network. Hubs are evolutionary conserved so they are slow evolving in nature but shows rapid turnover and regulation. They possess primal role in various biological functions in many ways and are responsible for many disorders like cancer, autoimmune disorders, and neurodegenerative disorders 5 among them; the most common is Parkinson's disease.

Parkinson's disease is a high-risk neurodegenerative disease with symptoms of involuntary tremors of the hand and head, muscle rigidity, slow movement and imbalance of posture [6]. The main pathological causes of Parkinson's disease ascribe to the loss of dopamine neurons in the basal ganglia [7], which consists of the striatum, globuspallidus (GP), subthalamic nucleus (STN), compacta (SNc), and reticular (SNr) structure of the substantianigra [8–10]. The loss of dopamine neurons causes beta oscillations ranging from 13 Hz to 30 Hz in the basal ganglia [11, 12].

Alpha-synuclein is a synuclein protein of unknown function primarily found in neural tissue, making up as much as one percent of all proteins in the cytosol of brain cells [13]. It is predominantly a neuronal protein expressed in the neocortex, hippocampus, substantianigar, thalamus, and cerebellum, but can also be found in the non-uronal glialcells [14]. In melanocytes. α-Synuclein is a presynaptic neuronal protein that is linked genetically and neuropathologically to Parkinson's disease. The main fact is that people with Parkinson's disease first start experiencing symptoms later in the course of the disease because a significant amount of the substantia nigra neurons have already been lost or impaired due to the accumulation of abnormal alpha-synuclein found in substantia nigra neurons. It is a hub protein belonging to SNCA. Along with this DJ 1 (4RKW) and Parkin (5C32) also plays a major role in parkinson's disease. The most widely prescribed pharmaceuticals for the treatment of Parkinson's disease include levodopa, carbipoda, rotigotine, amantadine, benztrophine, trihexyphenidyl, pramipexole, rapinirole, rasagiline, safinamide, seligiline, and sinemet. There are numerous studies on Parkinson's disease and its medications. Through this work, the public will become aware of the hub proteins responsible for Parkinson's disease as well as how medications interact with the hub proteins. The docking process is carried out with the aid of Discovery Studio to determine which drug reacts with hub proteins most frequently. After docking, the compound with the highest libdock score is selected and its stability analysed with the help of GROMACS molecular dynamic simulation tool. Parkin, DJ 1 and SNCA are responsible for Parkinson's disease. Since SNCA's crystal structure is not one of them, modelling SNCA using Phyre 2 is done before proceeding with docking.

Thymine, Guanine, Adenine, and Cytosine are the names of the four nitrogenous base types found in the human genome. Genome can be classified into genes and non-coding junk sequences. The GC content regions spam both coding and non-coding regions, hence they are crucial for both protein synthesis and gene expression. The huge regions in the human genome have GC-rich domains called isochores and took part in constructing some vital genes too.

The higher GC-rich repetitive areas are denoted as 'CpGisland' which also have a definite role in the development of disease. The CpG islands are usually located in gene exons, introns, 5'UTR, and 3'UTR regions and in the non-coding sequences. Higher GC content has higher thermal stability, while lower GC content has low thermostability. DNA with more GC content is highly stable due to the presence of more hydrogen bonds. The GC-rich regions have a definite role in gene regulation, gene expression, genome functionality, and disease development. Besides, high G and C nucleotides make it hard for primers to amplify the target DNA. It is suggested to select GC regions between 40 to 60 %, ideally 45%, while designing primers [15]. The GC regions have a unique role in DNA sequencing, such as gene structure also useful in gene mapping. Analysis of GC-rich regions useful to identify, study and characterize genetic disorders. In this work, we concentrated on SNCA, DJ1 and parkin.

Python was used to confirm the stability of DJ1, SNCA, and parkin after molecular dynamic simulation revealed that the DJ1-safinamide molecule is more stable. For that, we require a nucleotide sequence with the bases A, T, G, and C. The presence of GC in this sequence denotes stability, and the more GC there is the more stable the sequence will be. With the use of Biopython, this study also tests protein stability.

MATERIALS AND METHODS:

PubChem: Pubchem is a repository of chemical compounds; it contains detailed information on chemical compounds and their biological activities, so it is also known as a chemical database. It is a freely available database that provides more information about compounds, their chemical name, structure, properties, and biological activities. It also helps to download the chemical compound structure in SDS format and is very useful while docking. PubChem is a primary, most important chemical information resource for biomedical research fields such as cheminformatics, chemical biology, medicinal chemistry and drug discovery process. It is available in https://pubchem.ncbi.nlm.nih.gov/

PDB: Protein Data Bank is a repository of three-dimensional protein structures. The 3D structure and related data typically obtained by x-ray crystallography, NMR spectroscopy, and cryo-electron microscopy was deposited in this database. It is available freely at https://www.rcsb.org/. The RCSB PDB helps to search information under the PDB header, including information on the protein extraction method, experimental details, Molecular description, Primary citation, and physical and chemical properties of proteins. It also provides analysis tools that help measure the bond length and angle and identify structural features. One can search for their protein of interest using PDB ID, protein name, author name, sequence of interest, and particular ligand of interest. It also helps to download the 3D structure of a protein in .pdb format, which is very important for the docking and drug-designing process.

Uniprot: Uniprot, a universal protein resource, is a comprehensive resource for protein sequence and their features. The primary mission of this database is to support biological research by maintaining high-quality data. It is a stable, comprehensive, fully classified accurately annotated protein sequence with extensive cross references and a querying interface freely accessible to the public. Uniprot knowledge base (Uniprot KB), TrEMBL, and UniRef (Uniprot non-redundant references)are combined in the UniProt consortium. It provides detailed information on protein sequences, their features, molecular description, sequence length, source organism, and family. We can easily access the data by using the accession number, identification number, or protein name. It is freely available at https://www.uniprot.org/.

Phyre 2: Phyre 2 is a web-based bioinformatics tool that predicts and analyzes protein structure, function, and mutations. It is widely used for homology modeling. Phyre 2, uses advanced homology detection methods to build 3D models, predict ligand binding sites, and analyze the effect of amino-acid variants. We can directly submit the sequence for modelling. While submitting a protein sequence, the Phyre2 interprets the secondary and tertiary structure of their models, their domain composition, and model quality. This tool is available at http://www.sbg.bio.ic.ac.uk/phyre2.

Discovery Studio: Discovery Studio is a complete modelling and simulation software mainly used by Life Science researchers. It is an Interactive, visual and integrated software. It is mainly used for visualization, protein modeling, simulations, docking, pharmacophore analysis, QSAR, and library design. This software access computational servers and tools, share data, monitors jobs, and accurately prepare and communicate their project progress. Molecular docking, ADMET prediction a Lipinskifilteration can be done using discovery studio.

Discovery Studio Visualizer: Discovery studio visualizer is mainly used to visualize the protein structure and help interpret results. It helps to Visualize and examine very large macromolecule systems using a wide range of display types. It also supports a range of stereo graphical options. It is an afeature-rich molecular modeling application for viewing, sharing, and analyzing protein

Swissparam: Swissparam is a tool that computes various physical and chemical parameters for a

particular protein. The computed parameters include molecular weight, amino acid composition, atomic composition, extinction coefficient, instability index, aliphatic index, and grand average of hydropathicity.

Gromacs: Gromacs is a free, open-source molecular dynamics simulation package. It provides a rich set of calculation types, preparation, and analysis tools. The GROMACS was started in 1991 at the Department of Biophysical Chemistry, University of Groningen, Netherlands (1991–2000). Its name was originally derived from (GROningenMAchine for Chemical Simulations). GROMACS is operated with the help of a command-line interface.

It provides calculation progress and estimated time of arrival (ETA) feedback, a trajectory viewer, and an extensive library for trajectory analysis. In also support for different force fields, which makes GROMACS very flexible. It can be executed in parallel or as threads. It contains a script to convert molecular coordinates from Protein Data Bank (PDB) files into the formats it uses internally.

Biopython: The Biopython Project is an international association of developers of freely available Python (https: //www.python.org) tools for computational molecular biology. Python is an object-oriented, interpreted, flexible language that is becoming increasingly popular for scientific computing. Python is easy to learn, has a very clear syntax, and can easily be extended with modules written in C, C++ or FORTRAN [16].

The Biopython website (http://www.biopython.org) provides an online resource for modules, scripts, and web links for developers of Python-based software for bioinformatics use and research. Biopython aims to make it as easy as possible to use Python for bioinformatics by creating high-quality, reusable modules and classes.

Biopython features include parsers for various Bioinformatics file formats (BLAST, Clustalw, FASTA, Genbank), access to online services (NCBI, Expasy), interfaces to common and not-so-common programs (Clustalw, DSSP, MSMS), a standard sequence class, various clustering modules, a KD tree data structure *etc.* and even documentation [17]. The latest release is Biopython 1.79.

Methodology:

Docking Using Discovery Studio: Uniprot, Protein Data Bank (PDB), PubChem and NCBI were the main online databases used for the investigation. Molecular docking was performed using Discovery Studio (v 21.1.0.20298). The crystallographic structure of Alpha-synuclein was not available; As a result, Phyre2 was used to model the Alpha-synuclein protein.

Crystal structure of DJ-1 (PDB ID: 4RKW) and constitutively active Sin recombinase catalytic domain I100T (PDB ID: 5C32) were downloaded from Protein Data Bank. Before protein preparation, hetero atoms and unwanted chains are removed. The protein preparation protocol was run using Discovery Studio version 21.1.0.20298. Protein preparation steps involve protonation, optimization of side-chain conformation, and loop modelling.

Levodopa, carbipoda, rotigotine, amantadine, benztrophine, trihexyphenidyl, pramipexole, rapinirole, rasagiline, safinamide, seligiline and sinemet are the synthetic drugs currently used for Parkinson's disease and their 3D structures were retrieved from the PubChem database. The selected compounds were prepared according to the Discovery studio's ligand preparation protocol for removing duplicates, enumerating isomers and tautomers.

Molecular docking was done by defining the active site as Receptor Cavity and Direct/Site specific. The receptor cavity method will derive the binding site from the cavity of the protein structure. In the Direct/Site-specific method, we can define the protein's binding site from a literature review or using other online resources. Docking was performed using the LibDock tool as it allows flexibility. Usually, LibDock is used for the library docking of compounds. Binding Energy Calculation of docked complexes was done using DS. From molecular docking, the most active compounds with the least binding energy were screened and underwent further predictions.

Admet Prediction: Biological activity prediction was made using Lipinski's rule of filter and

ADMET prediction, which is used to check the molecules' drug-likeliness. Calculated the number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA), molecular weight (MW) in Dalton(Da), and log value of octanol-water partition coefficient (AlogP) using Lipinski's rule of filter. According to Lipinski's rule, an orally active drug should have HBD ≤ 5; HBA ≤ 10; MW ≤ 500 Da; AlogP ≤ 5. Performed computational prediction of pharmacological features based on the chemical structure of molecules using 'ADMET descriptors', a comprehensive suite of DS. Intestinal absorption, aqueous solubility, blood-brain barrier penetration, plasma protein binding, cytochrome P450 2D6 inhibition, and hepato-toxicity are the parameters of ADMET prediction.

Molecular Dynamic Simulation: Molecular dynamic simulation analysis interprets the binding affinity of the docked complex in a real system. Gromacs was used to perform dynamic simulations. The compound with high lib dock score was selected, and studied its simulation with the help of gromacs. The lowest energy valued, best pose from the docked complexes have opted for molecular dynamics via Gromacs 2021. The force field used was CHARMm 27. Used SWISSPARAM server for generating ligand topology. TI3P water model was used for solvation with a triclinic box. The system was subjected to energy minimization during MD by the steepest descent approach. The Particle Mesh Ewald (PME) method was employed to calculate electrostatic interaction, and the linear constraint solver (LINCS) algorithm was used for predicting Van der Waals interactions. 300K was the standard temperature the modified Berendsen thermostat kept and the pressure was set by the Parrinello-Rahman coupling method. Finally, a 100ns molecular dynamics simulation was carried out for the complex. The MD trajectory analysis explored the Root Mean Square Deviation (RMSD) and Fluctuations (RMSF).

To Calculate GC Content: For the programming, Python language is used version Python 3.7.9 [18] with the operating system Windows 10 (64-bit OS, x64-based processor) and Biopython version 1.79. Along with Notepad ++ as editor. To calculate the GC percentage, we used Bio.SeqIO to parse the FASTA file and compile a list of all the GC percentages for the proteins DJ1, SNCA, and Parkin, which have an important role in parkinson disease. Bio.SeqIO.parse() is used to read in-sequence data as SeqRecord objects. Function returns as an iterator which gives SeqRecord objects using loop [19]. Then the sequence of each protein is assigned to a variable, the GC Content for each sequence is calculated using the formula mentioned below. FASTA file 'fasta_seq.fasta' is given as input file, which has the details DNA sequence of the proteins DJ1, SNCA and Parkin

GC-content is usually expressed as a percentage value but sometimes as a ratio (called G+C ratio or GC-ratio). The GC-content percentage is calculated as [20].

$$\text{GC content} = (G + C / A + T + G + C) * 100\%$$

RESULTS AND DISCUSSION: Discovery Studio's ligand preparation protocol generated all possible synthetic drug stereoisomers. A total of seven synthetic compounds showed better LibDock score, Binding energy and Complex energy in both Receptor Cavity and Direct docking methods. Levodopa showed better intermolecular interaction with 4RKW and 5C32. Safinamide showed better efficacy (111.577 kcal) with 4RKW in the direct method. The interactions include conventional hydrogen bonds, carbon-hydrogen bond, unfavorable positive-positive bond, pi-sigma, pi-pi T- shaped and pi-Alkylbond.

The pharmacological potential of the synthetic drugs was examined using ADMET and Lipinski's rule of filtering in Discovery Studio; hence, it will help to avoid late-phase defeat in clinical trials. Levodopa showed optimal solubility, BBB penetrability, and intestinal absorption with no hepatotoxicity. Pramipexole also satisfied all these criteria of ADMET predictions. Safinamide and Dopamine showed hepatotoxicity.

The molecular docking studies and ADMET predictions found that Levodopa and pramipexole passed all parameters and showed good interaction where Levodopa could bind with both 4RKW and 5C32. Safinamide showed the highest libdock score of 111.577 kcal/mol in the direct docking method with 4RKW. Hence, did the binding stability of the docked complex. In the Direct method, Levodopa was stabilized with both 4RKW and 5C32 by four

conventional hydrogen bonds. In the Receptor Cavity method, Levodopa shared two conventional hydrogen bonds with 4RKW and three conventional hydrogen bonds with 5C32. Also, they showed good binding energy and complex energy. The molecular dynamics simulation using Gromacs 2021 was performed to examine the structural stabilities of target proteins with its top-ranked ligand. Here, the results of the MD simulation for the ligand-protein complex are analyzed for 100ns. The RMSD (Root Mean Square Deviation) and RMSF were obtained from the trajectory files. The low RMSD value correlated with high structural stability. The present work observed that the complex was stable with an RMSD of 0.125nm throughout the simulation. RMSF represents the residues fluctuation in the complex. Here, the complex showed fluctuation within 0.35nm. The extreme fluctuation was observed at the C-terminal ~0.33nm. Other fluctuations found at the 47th, 49th, 130th, and 160th positions are 0.14nm, 0.15nm, 0.175nm and 0.135nm, respectively.

TABLE 1: DETAILS OF SYNTHETIC DRUG COMPOUNDS DOCKED TO PARKINSON'S DISEASE HUB PROTEINS

Sl. no.	Protein (PDB ID)	Compound	LibDock Score	Binding Energy	Complex Energy	Interacting Residues
1	4RKW [DJ 1] (RC: S1)	Levodopa	79.5106	-25.775	-8025.8062	Arg 98, Tyr 67, Lys 62, Pro 66
		Pramipexole	76.4063	-34.767	-7822.4499	Lys 62, Gln 95, Tyr 67, Glu 94, Pro 66, Ile 91
		Rasagiline	79.5309	-61.225	-7860.5187	Glu 94, Lys 62, Pro 66, Ile 91
		Sinemet	72.8062	-36.913	-7933.5707	Lys62, Gly 65, Gln 95, Lys 62, Pro 66, Ile 91
	Direct method	Levodopa	86.021	-3.7736	-7991.9230	Leu 38, Gly 40, Gln 45,Asp 42, Gly 37, Val 44, Ala 39
		Safinamide	111.577	-42.429	-7970.2777	Ser 47, Gln 45, Cys 46, Gly 13, gly 75, Pro 158, Leu 77, His 126, Cys 106
2	5C32 Parkin (RC)	Levodopa	80.79	-83.483	-4540.6626	Lys 110, Asp 111, Lys 107, Lys 82
	Direct method	Levodopa	62.4915	-75.524	-4543.2609	Arg 47, Ser 36, Arg 66, Glu 124, Arg 69
3	SNCA (RC)	Pramipexole	79.1981	-309.94	-6452.4029	Glu 130, Glu 126, Asp 135, Pro 128, Glu 132, Tyr 133
		Rasagiline	73.2044	-109.08	-6330.5979	Glu 130, Glu 126, Met 127, Pro 128, Glu 132, Tyr 133
		Rapinirole	82.6228	-21.026	-5819.7479	Asp 135, Glu 131, Tyr 125, Met 127
		Seligiline	73.3577	-37.08	-6238.0617	Gly 132, Asp 135
		Sinemet	62.9585	-141.54	-6379.6775	Glu 130, Asp 135, Pro 128, Met 127

*Molecular docking of synthetic drugs to hub proteins of Parkinson's disease using Discovery Studio version 21.1.0.20298. Residues forming hydrogen bonds are highlighted. RC: Receptor Cavity, S: Site.

TABLE 2: ADMET PREDICTION OF SELECTED 7 SYNTHETIC COMPOUNDS

Sl. no.	Ligand	Solubility Level	BBB Level	CYP2D6 Prediction	Hepatotoxic Prediction	Absorption Level	PPB Prediction
1	Levodopa	4	3	False	False	0	False
2	Pramipexole	3	2	False	False	0	False
3	Rasagiline	3	1	False	False	0	True
4	Ropinirole	3	1	False	False	0	True
5	Safinamide	3	2	False	True	0	True
6	Selegiline	3	0	False	False	0	True
7	Sinemet	4	3	False	True	0	False

ADMET parameter assessment for NSAIDs using ADMET protocol of Discovery studio version 4.0 was done. The parameter range is given below. Solubility: 0- extremely low, 1-low but possible, 2- possible, 3- good, 4- optimal, 5- too soluble; Intestinal absorption: 0- good, 1- moderate, 2- poor, 3- very poor; BBB level: 0-very high penetrant, 1- high penetrant, 2 -medium penetrant, 3 – penetrant, 4 –undefined (BBB: Blood-brain barrier; CYP2D6: Cytochrome P450 2D6; PPB: Plasma protein binding).

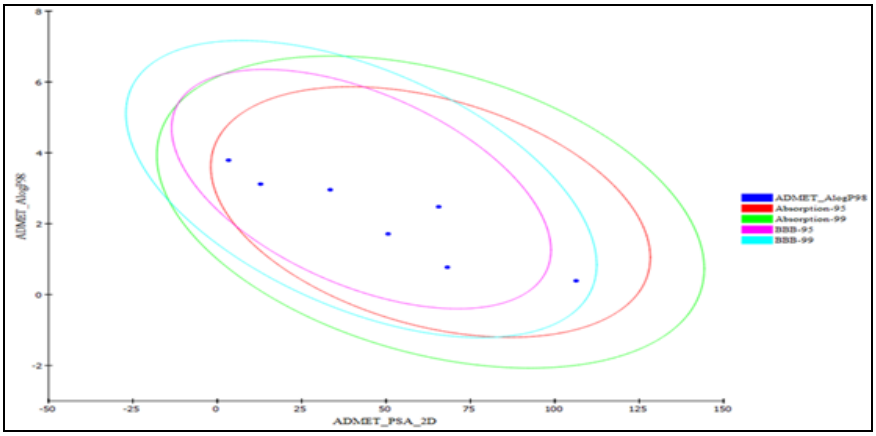

FIG. 1: PLOT OF POLAR SURFACE AREA (PSA) VS. LOGP SELECTED FOR SYNTHETIC DRUGS

ADMET Plot for Levodopa, Pramipexole, Rapinirole, Rasagiline, Safinamide, Seligiline, Sinemet displaying 95% and 99% confidence limit ellipses corresponding to the blood-brain barrier (BBB) and the human intestinal absorption models in ADMET_AlogP98.

TABLE 3: MOLECULAR DESCRIPTORS OF SELECTED 7 SYNTHETIC COMPOUNDS ACCORDING TO LIPINSKI FILTER

Sl. no.	Ligand	HBA	HBD	MW	AlogP	RB
1	Levodopa	5	5	197.188	-2.089	3
2	Pramipexole	3	5	213.343	0.244	3
3	Rapinirole	3	2	261.382	1.398	7
4	Rasagiline	1	2	172.246	1.888	2
5	Safinamide	4	4	303.351	1.247	7
6	Seligiline	1	1	188.289	2.233	4
7	Sinemet	3	5	154.186	-0.232	2

The molecular descriptors of 7 synthetic drugs were evaluated using Lipinski filter of Discovery studio version 4.0. The criterion for Lipinski filter is; MW</ = 500 Da, HBD</ = 5, HBA</ = 10, AlogP</ = 5, RB</ = 5 (HBA: H-Bond Acceptors; HBD: H-Bond Donors; MW: Molecular Weight; AlogP: octanol-water partition coefficient).

Molecular Dynamic Simulation: RMSD versus time plot during 100 ns MD simulation of 4RKW with the Safinamide. It is shown that the structures were stable after 2 ns.

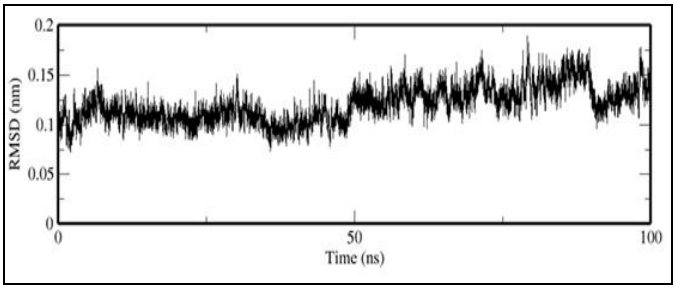

FIG. 2: RMSD (ROOT MEAN SQUARE DEVIATION) PROFILE OF DOCKED COMPLEX

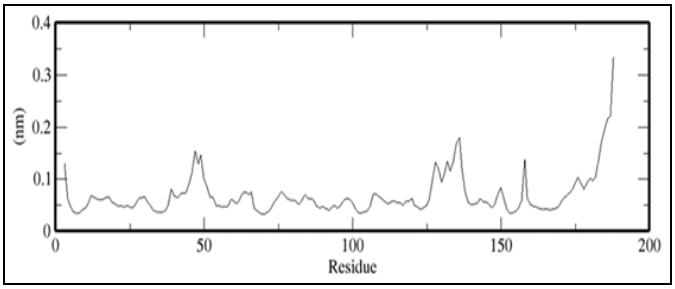

FIG. 3: RMSF (ROOT MEAN SQUARE FLUCTUATION) OF RESIDUES OF PROTEIN

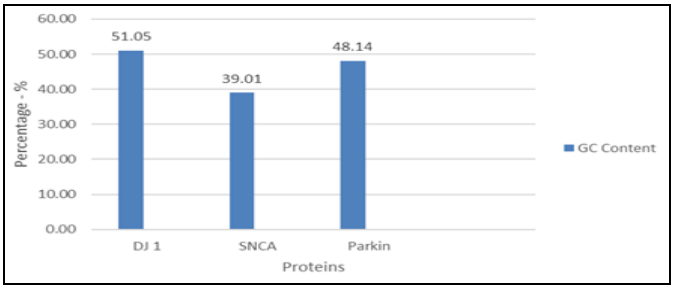

FIG. 4: STABILITY ANALYSIS OF THE SELECTED PROTEIN ON THE BASIS OF GC CONTENT

CONCLUSION: The *in-silico* molecular docking study is beneficial in understanding the intermolecular interaction between protein and drug. The current study aimed to analyze the intermolecular interaction between the protein of Parkinson's disease and the selected synthetic drugs. Took the results based on the highest lib dock score and binding energy calculation. It is concluded that Levodopa exhibits good interaction

and binding affinity with 4RKW and 5C32; it also satisfies all the parameters of ADMET and Lipinski's rule of filtering. Safinamide showed the highest dock score and good binding affinity with 4RKW.

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CONFLICTS OF INTEREST: Nil

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