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IN-SILICO MOLECULAR DOCKING INSIGHTS OF BIO ACTIVE COMPOUNDS OF GENUS MOMORDICA AND NOVEL SYNTHETIC ANTI –PARKINSON'S DRUG: A PROMISING LEAD IN THE QUEST FOR MAO-B INHIBITORS

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Keywords:

MAO-B inhibitors, *In-silico* molecular docking, Synthetic anti-parkinson's drugs, Bioactive compounds in *Momordica* species, Folic acid

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ABSTRACT: Discovering Novel MAO-B inhibitors is promising therapeutic strategy for Parkinson's disease. The pharmacological effects of MAO-B inhibitor showed significant neuro-protection and improved motor function and reduced oxidative stress marker. *In-silico* molecular docking simulation to investigate the interaction between target protein (MAO-B Inhibitors) and revealing promising hits with high binding affinity and favorable interactions. Molecular docking and binding affinity were analyzed between protein MAO-B inhibitor with selected bioactive compounds and Synthetic drugs in order to find the most potential inhibitor against the target. Thus, the objective of this research can provide an insight comparision based prediction towards some bioactive compounds in Genus *momordica* species (folic acid, momordicin, Balsaminol-A, Karavilagenin-C, Beta carotene) and few synthetic drugs (Opicapone, Apomorphine, Selegiline, Rasagiline, Ladostigil Zonisamide, Safinamide, NSAID, RG-2833 (gene therapy drug) against MOA-B Inhibitors performed using Pubchem, ProteinDataBank, Biovia discovery studio and PyRx. This research focuses on docking between the potential bioactive compounds shows strong affinity towards the targeted MOA-B inhibitor protein to treat parkinson's diseases compared to synthetic drugs. This study shows the Folicacid binding score (-10.9 kcal/mol) indicate stronger binding affinity compare to novel synthetic anti-parkinson's drugs. It concluded that Folic acid is a neutragenomic potential to 'tame' MAO-B activity and prevent neurodegeneration in brain.

INTRODUCTION: Parkinson's disease a stealthy and relentless foe, strikes without warning, leaving a trail of tremor, rigidity and uncertainity in its wake. As the second most common debilitating neurodegenerative disorder. In addition to classic motor symptoms, non- motor manifestations (such as rapid eye movement sleep disorder, anosmia, constipation and depression) appear at prodromic/ premotor stage and evolve, along with cognitive impairment and dysautonomia, as the disease progresses, often dominating the advanced stages of the disease [1]. The key molecular pathogenic mechanisms include α-synuclein, misfolding and aggregation, mitochondrial dysfunction, impairment of protein clearance (associated with deficient ubiquitin-proteasome and autophagy-lysosomal systems), neuroinflammation and oxidative stress.

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The involvement of dopaminergic as well as noradrenergic, glutamatergic, serotonergic and adenosine pathways provide insights into the rich and variable clinical phenomenology associated with PD [2]. Monoamine oxidase-B (MAO-B) is an enzyme in the body that breaks down several chemicals in the brain, including dopamine. An MAO-B inhibitor makes more dopamine available to the brain. This can modestly improve many PD

movement symptoms. MAO-B inhibitors may be useful as early monotherapy (a medication used alone) or as an add-on to other medications, including levodopa. When used with other medications, MAO-B inhibitors may reduce motor fluctuations periods of diminished symptom control as a levodopa dose wanes minimizing "off" time and extending "on" time [3]. Nutraceutical attributes of *momordica* species-A potential tropical bioresources. It belongs to the family of Cucurbitaceae [4]. The *momordica* species such as *M. charantia*, *M. balsamina* (Linn), *M. dioica* (Roxb), *M. cochinchinensis* (Spreng), and *M. tuberosa* or *cymbalaria* exploring nutritional and nutraceutical properties [5]. The bioactive compounds such as phenolic acids, flavonoids, carotenoids cucurbitane triterpenoids, and phytosterols [6].

By elucidating the Molecular Docking mechanism aims to uncover new avenues for the development tool it is on the front line of computational biology and drug discovery the explosion of structural and chemical information in recent years has rendered this use the computation approaches to discover developed and analyzed and similar biologically active molecules the computer aided drug discovery leads to virtual screen, energy calculations and drug interactions this helps in scientists in minimizing the synthetic and biological testing. Docking plays an important role in predicting the orientation of the ligand. The ligand is searched in a six dimensional rotational or translational space to fit in the binding site. It plays a crucial role in predicting the interactions of small molecules (ligands) with the binding site of a protein of interest [7]. PyRx includes docking wizard with an easy-to-use user interface which makes it a valuable tool for Computer-Aided Drug Design. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engine that are essential for structure-based drug design. It decreases both the time and resources required to test the whole database experimentally, by selecting only the most promising ones [8]. Molecular visualization is a key aspect of the analysis and communication of modeling studies. It is a graphics visualization tool for viewing, sharing, and analyzing protein and modeling data using Biovia Discovery Studio Visualizer for interactive 3D visualization [9].

FIG. 1: *MOMORDICA* SPECIES

***In-silico* Molecular Docking:** Molecular docking helps us in predicting the intermolecular framework formed between a protein and a small molecule or a protein and protein and suggest the binding modes responsible for inhibition of the protein. To accurately carry out docking studies one requires the high-resolution X-ray, NMR or homology-model structure with known/predicted binding site in the biomolecule (PDB). Docking methods fit a ligand into a binding site by combining and optimizing variables like steric, hydrophobic and electrostatic complementarity and also estimating the free energy of binding (scoring) affinities. Finding the optimum binding mode of ligand to receptor site is the main objective of docking. Molecular docking is a common method employed in structure-based drug design.

It is used in drug discovery to elucidate potential actions of uninvestigated bioactive compounds by identifying their molecular targets using bioinformatics along with systems biology approaches. It predicts how proteins interact with small chemical molecules or ligands to form a stable complex. In drug design and drug discovery the usefulness of molecular docking cannot be overemphasized [10]. The PyRx has built-in AutoDock, AutoDock Wizard, Vina Wizard, and Open Babel. Steps involved in:

Step I - Preparation of Protein: From Research Collaboratory Structural Bioinformatics Protein data bank (PDB) downloading the 3D-structure of the Protein. After that downloaded structure should be pre-processed. From removal of the water molecules, the charges stabilization, missing residues filling, add hydrogen atom side chains generation [11].

Step II – Ligand Preparation: By using Pub Chem Ligands molecule can be downloaded.

Step III- PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. Using that Grid Generation performed. In this site, rotatable group, excluded volumes, constraints kept constant. Operations performed (crossover, migration, mutation) is the key parameter in determining. Binding Cavity Prediction are to be done [12].

Step IV – Prediction of Active site: site of protein molecule should be predicted after that Preparation of protein, the water molecules and hetero atoms if present they are removed from cavity.

Step-V-Docking: Ligand and protein interactions are analysed [13].

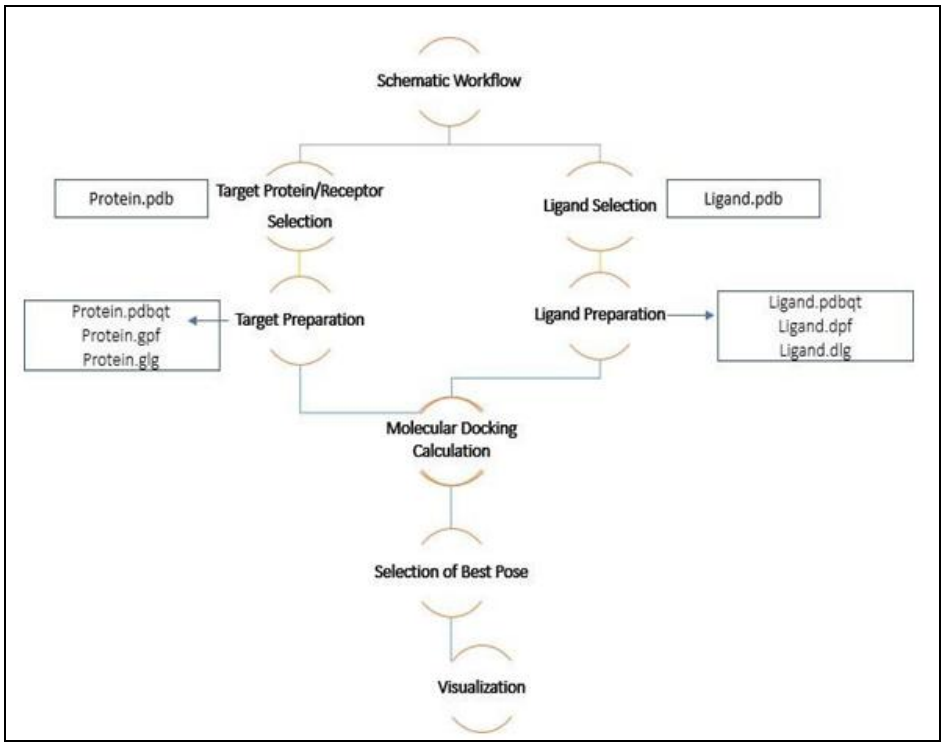

FIG. 2: SCHEMATIC WORKFLOW OF MOLECULAR DOCKING PROCEDURE

Drug Profile:

TABLE 1: DRUG PROFILE

Protein selection (Receptor target) Mono Amino Oxidase-B inhibitor
Ligands Selection: (a) Bio Active compound from Momordicia species such as Folic acid, Beta-carotene, Momordicin. (b) Synthetic Anti-Parkinson's drugs are Apomorphine (Anti-Parkinson's Drug), Zonisamide (Anti-Convulsant), Ibufrofen, Paracetamol, Aspirin, Diclofenac flurbiprofen (NSAID), Safinamide, RG2833 (Brain Penetrant Histone Di-Acetylase Inhibitor), Opicapone (COMT Inhibitor) Ladostigil(Anti-Parkinson's Drug) (c) Standard/reference MAO-B Inhibitor Seligiline, Rasagiline

Ligand Preparation Using Pub Chem: Pub Chem is an open chemistry database at the National Institutes of Health (NIH).

TABLE 2: LIGAND- PUBCHEM ID

Sl. no.	Ligand	Pub Chem ID	Sl. no.	Ligand	Pub Chem ID
1	Opicapone	135565903	10	Beta-carotene	5280489
2	Safinamide	131682	11	Folic acid	5398658
3	RG-2833	56654642	12	Ladostigil	208907
4	Apomorphine	6005	13	Balsaminol-A	44607276
5	Flurbiprofen	3394	14	Karavilagenin-C	46182790
6	Zonisamide	5734	15	Paracetamol	1983
7	Selegiline	26757	16	Ibuprofen	3672
8	Rasagiline	3052776	17	Aspirin	2244
9	Mormordicin	57518366	18	Diclofenac	3033

Protein Preparation Using PDB: The Protein Data Bank (PDB) is a database for the three-dimensional structural data of MAO-B Inhibitor Receptor is our chosen protein for molecular docking.

TABLE 3: PROTEIN- PDB ID

S. no.	Protein	PDB ID
1.	MAO-B Inhibitor	1GOS

Refinement of Receptor Proteins: Protein structures of receptor proteins were refined using Discovery Studio Visualiser software before docking studies. All the proteins had co-crystallized ligands (X-ray ligand) and water molecules in the binding site. The ligands and water molecules enclosed in each protein structure were removed from the binding site using Discovery Studio Visualizer software and saved as pdb format to a new file.

This is a molecular application app that is used viewing, sharing, analyzing protein and small molecular data. This app helps with the 3d visualization of the Ligand target interaction Preparation of Target Protein or Receptor. After successful downloading of ligand and protein files, next step is the preparation of pdbqt format files of both protein as well as ligand. Pdbqt file for ligands can also be generated using OPEN BABEL used for preparation of PDBQT files of both Protein and ligand (protein.pdbqt, ligand.pdbqt) using PyRx [14].

Scoring Function: Molecular docking programs use scoring functions to estimate the binding energetics of the predicted ligand-receptor complexes.

The energy variation, due to the formation of the ligand-receptor structure, is given by the binding constant (Kd) and the Gibbs free energy (ΔGL) Prediction of the binding energy is performed by evaluating the most important physical-chemical phenomena involved in ligand-receptor binding, including intermolecular interactions, desolvation and entropic effects therefore, the greater the number of physical-chemical parameters evaluated, the greater the accuracy of the scoring function [15].

RESULTS: In this protocol, accessing the protein and ligand structure, identifying the active site grid box coordination, generation of required files, execution of docking, selection of best docked pose and binding interaction, all step are illustrated in simple possible way for demonstration and execution process. Binding affinity of drugs represented in negative values shown higher affinity using PyRx software.

TABLE 4: NEWER THERAPEUTIC DRUG FOR TREAT PARKINSON'S DISEASE AND ITS PUB CHEM ID AND BINDING SCORES

Sl. no.	Ligand	PUB CHEMID	Binding Score-Kcal/mol	Sl. no.	Ligand	PUB CHEM ID	Binding Score-Kcal/mol
1	Opicapone	135565903	-9.8	11	Betacarotene	5280489	-8.1
2	Safinamide	131682	-9.4	12	Folic acid	5398658	-10.9
3	RG-2833	56654642	-9.3	13	Balsaminol-A	44607276	-6.9
4	Apomorphine	6005	-9.9	14	Karavilagenin-C	46182790	-7.2
5	Ladostigil	208907	-6	15	flurbiprofen	3394	-9.3
6	Zonisamide	5734	-8.1	16	Ibuprofen	3672	-8.1
7	Selegiline	26757	-7.3	17	Aspirin	2244	-7.5
8	Rasagiline	3052776	-7.8	18	Diclofenac	3033	-8.1
9	Mormordicin	57518366	-7.7				
10	cucurbitacean-B	5281316	-6.8	19	Paracetamol	1983	-6.3

In this table only two which have more binding capacity to receptor, high binding affinity score selected for future references.

TABLE 5: THESE DRUGS ACT AS THERAPEUTIC POTENTIAL FOR PARKINSON'S DISEASE

Sl. no.	DRUG	Binding Score
1	Folicacid	-10.9 kcal/mol
2.	Apomorphine	-9.9 kcal/mol

In our studies for folic acid and apomorphine both have more affinity compare to all other drugs revealed for 3d structure of ligand receptor interaction visualized using Biovia discovery app.

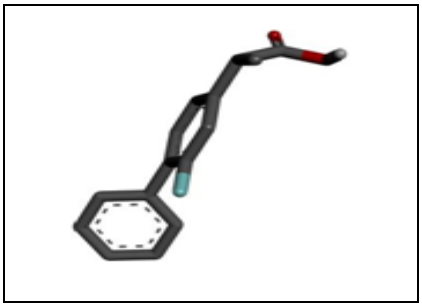

FIG. 3: FOLICACID PDB DOCKED STRUCTURE

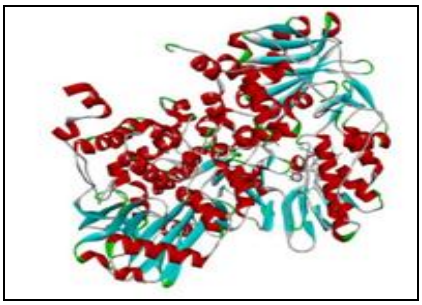

FIG. 4: FULL 3D STRUCTURE OF FOLIC ACID AS A LIGAND INTERACT WITH MAO-B INHIBITOR AS A PROTEIN VISUALIZED USING BIOVIA DISCOVERY APP

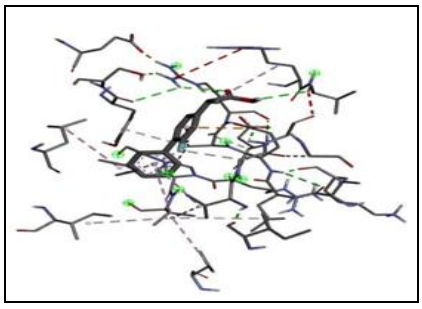

FIG. 5: FOLICACID -3D LIGAND- PROTEIN INTERACTION

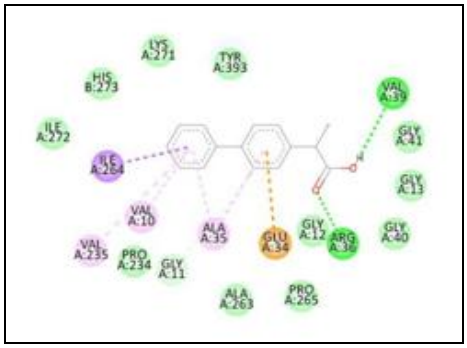

FIG. 6: FOLICACID- 2D DIAGRAM OF LIGAND-PROTEIN INTERACTION

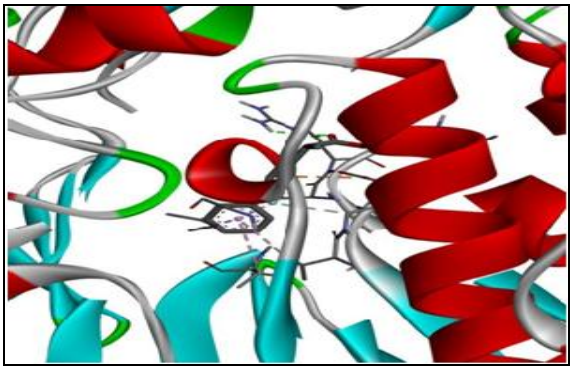

FIG. 7: IT SHOWED THAT FOLIC ACID INTERACTION WITH MAO-B INHIBITOR 3D STRUCTURE.

FIG. 8: APOMORPHINE PDB DOCKED

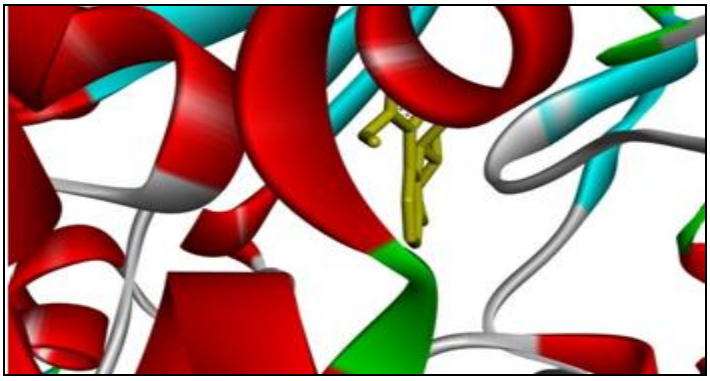

FIG. 9: APOMORPHINE INTERACT WITHMAO-B3D STRUCTURE

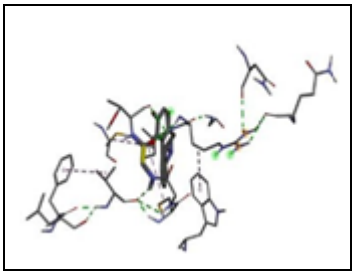

FIG. 10: APOMORPHINE AS A LIGAND INTERACT WITH RECEPTOR/PROTEIN MAO-B INHIBITOR

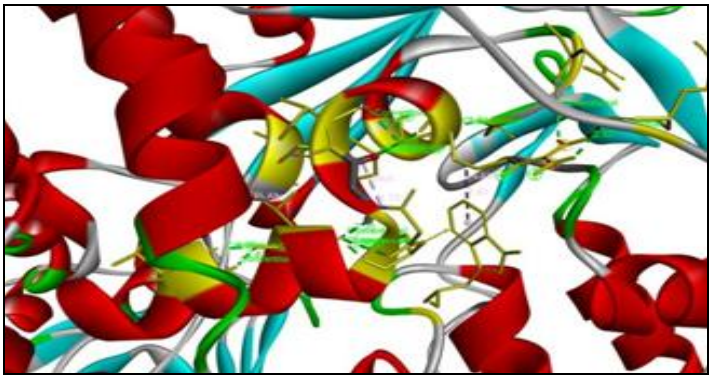

FIG. 11: APOMORPHINE AS A LIGAND ON MAO-B INHIBITOR

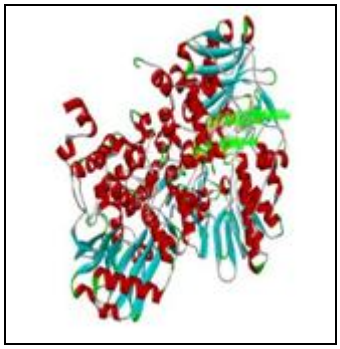

FIG. 12: APOMORPHINE INTERACT WITH MAO-B INHIBITOR

DISCUSSION: Folic acid present in *Momordica* species exhibits high binding affinity for MAO-B, outperforming existing inhibitors. Comparison with synthetic drugs used for anti- parkinson's drugs and Bioactive components, Folic acid has shown remarkably high binding affinity in docking studies making promising candidate for further research and potential therapeutics inhibit MAO-B activity compare to synthetic drugs. The Binding score of molecular docking represents in negative value according to that higher negative value represents the higher binding affinity to receptor and also higher therapeutic value.

*** Bioactive Compounds of *Momordica* species binding Score against MAO-B Inhibitor:** This studies investigated in that bioactive components from *Momordica* species such as Folic acid (Pubchem id-5398658 and binding score is -10.9 kcal/mol), beta-carotene (Pubchem id -5280489 and binding score is -8.0 kcal/mol) and momordicin (Pubchem id-57578366 and binding score is -7.7 kcal/mol), cucurbitacean-B (Pubchem id – 5281316 and binding score is -

6.8 kcal/mol) Balsaminol-A- Pubchem id-44607276 and binding score is -6.9 kcal/mol) Cucurbalsaminol-A (Pubchem id-44607278 and binding score is -7.3 kcal/mol) Karavilagenin- C (Pubchem id-46182790 and binding score is -7.2 kcal/mol). Folicacid have promising avenue for Parkinson's therapy.

*NSAID Docking score against MAO-B Inhibitor: Long term administration of NSAID cross BBB will reduce the risk of Parkinson's disease. Flurbiprofen (Pubchem id -3394 and binding score is -9.3kcal/mol) Diclofenac (Pubchem id -3033 and binding score is -8.1 kcal/mol) Ibuprofen (Pubchem id -3672 and binding score is -8.1 kcal/mol) Paracetamol (Pubchem id - 1983 and binding score is -6.3kcal/mol) and Aspirin (Pubchem id -2244 and binding score is kcal/mol).

*Other synthetic drug against MAO-B Inhibitor: Apomorphine (Anti-parkinson's drug), Zonisamide (Anti-convulsant), RG-2833 (brain penetrant Histone Di-Acetylase inhibitor), Opicapone (COMT inhibitor) Safinamide, Seligiline, Rasagiline (Anti-parkinson's drug). The results shown that Apomorphine (-9.9kcal/mol) strong binding affinity to the active site of MAO-B Inhibitors compare to other synthetic drugs.

CONCLUSION: Molecular docking gives valuable insight into the binding affinity and interactions of ligand within the target protein. It investigates that folate present in natural compound

shows more binding affinity compared to novel synthetic anti-parkinson's drugs against MOA-B Inhibitors. The foregoing shows that *momordica* species is an promising therapeutic potential to treat neuro-degenerative disorder Parkinson's disease. However subsequent *in-vitro* and *in-vivo* assessments are necessary to validate the efficacy. The strong binding affinity of folic acid in docking studies highlights its potential as a valuable compounds for various biological and pharmaceutical uses.

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