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"THE EFFECT OF QUINOLINE AGAINST SYNCYTIN 1 FOR THE POSSIBLE TREATMENT OF MULTIPLE SCLEROSIS: A BIOINFORMATIC APPROACH"

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ABSTRACT

Multiple Sclerosis (MS)is a potentially disabling disease of the brain and spinal cord (CNS central nervous system). The immune system attacks the protective sheath (myelin) that covers nerves fibers and causes communication problems between the brain and rest of the body. Several ligands and targeted protein were analyzed for the cure of MS. All the information and studies were derived from molecular docking. It plays an important role in pharmaceutical research, in our study protein Syncytin 1 can binds with the natural compounds such as Benzimidazole, Quinoline, Nitroimidazole, Lidamycin. with the help of PyRx the binding affinity were determine. Quinoline was the best compound to bind with the protein having minimum binding energy. The software AutoDock Vina were used for the molecular docking. The outcome showed 9 poses with distinct binding energy and RMSD. Through PyMOL the ligand was analyzed. In this *in silico*study, it can determine that Quinoline shows the properties against the MS, the best binding affinity with syncytin 1 protein. Hence, Quinoline compound can take for the future studies for making a promising drug for the treatment of MS.

KEYWORDS: Multiple sclerosis, Myelin, Quinoline, Syncytin 1, Molecular Docking

I. INTRODUCTION

Multiple sclerosis (MS) is defined as the chronic autoimmune disease whichattacks the myelinated axons in Central nervous system and destroys the myelin with axons differently.It is a neurological inflammatorydisease which causes axonal loss, inflammation and reactiveastrologist whichleads to this demyelination in the CNS (Motavali et al., 2020).

MS is an organ specificT cell mediatedtwo stage disease which is followed by the early inflammation responsible for major relapsing–remitting disease and delayed neurodegeneration whichcausesnon-relapsingprogression, i.e. secondary and primary progressive MS(Dobson et al., 2019). There are two major forms of Multiple sclerosis (MS), acute neurological disease.First, Relapsing-remitting (RR)-MS, which is the mostfrequent (85%–90%) andmainly affects women about double as often as men.In many cases RR-MS patients later develop secondary progressive (SP)-MS as well. Whereas,About 10%–15% of patients present with insidious disease onset and steady progression, termed primary progressive (PP)-MS.(Sospedra et al., 2005).The main factors which contributes significantly to the overall development risk of the onset of Multiple sclerosis can be,Genetic predisposition, lifestyle, and environmental factors (Liguori et al., 2019).

Progressive MS is the term which can be defined as the which develops with the increase of neurological deficits in the absence of prior or intermittent exacerbations andremissions.This can bedistinctly different from the relapsing-remitting course of the disease which could be characterized by new bouts of the disease followed by clinical remission stages (Lassmann et al., 2019). Moreover, different studies have been conducted to put forward the specific explanatory for knowing how progressive multiple sclerosis gets triggered. Based on one study, brain damage can be driven by inflammatory processes which similar to RRMS, on the other handduring progressive stages of MS, a microenvironment gets created within the Central Nervous System(CNS), whichfavours homing and retention of inflammatory cellsand ultimately causing disease-modifying therapies to become largelyineffective (Correale et al., 2017). The pathogenic region of MS is believed to be located in the *brain medulla*,whereas The *kidney* controls the congenital constitution, like dizziness, and depression are caused by insufficiency of the *kidney* essence and *marrow sea* insufficiency syndrome. Some investigators support that *congenitall deficiency syndrome* is a key factor responsible for MS, and they show that most of the patients with MS have an empty *governor channel* and damage to the *kidney yang* and *brain marrow* (Peng et al., 2021). In all these symptoms and effects only traditional medicine has proven to be effective in controlling the sideeffects (Peng et al., 2021)

Furthermore, US Food and Drug administration (FDA) in October 2018 has approved near about 15 medications for managing and modifying the available treatments formultiple sclerosis.These are asfollows;

- Preparations of five interferon beta;
- Two preparations of glatiramer acetate;
- MAbs monoclonal antibodieswhich are first B cell targeted therapy such as, natalizumab, alemtuzumab, daclizumab, and ocrelizumab.
- Chemotherapeutic agent mitoxantrone; and
- The small – molecule oral agents fngolimod, dimethyl fumarate, and terifunomide(Li et al., 2020)

Herbal phytochemicals of medicinal plantshave shown their remedial effects in various diseases.Similarly,some of the therapeutic herbal plants with their derivatives such as., ; Ginkgo biloba, Zingiber officinale, Curcuma longa, Hypericum perforatum, Valeriana officinalis, Vaccinium macrocarpon, Nigella sativa,Piper methysticum, Crocus sativus, Panax

ginseng, Boswellia papyrifera, Vitis vinifera, Gastrodia elata, Camellia sinensis, Oenothera biennis, MS14 and Cannabis sativa are known for their therapeutic role in MS patients.Various drugshave also beenapproved and introduced forcuring this neurological disorder disease like MAbs basednatalizumab, alemtuzumab, daclizumab,fingolimod, glatiramer acetate and ocrelizumab. But unfortunately, these all drugs were partially ineffective over the affected patients.They also have shown adverse effects by intaking for prolonged use. One of the example ofunsuitability, are IFN-Beta consumption includingstroke, headache, migraine and depression. Until now,there isno absolute treatment available, which has been found for treating MS. Therefor, there is an emergentneed for finding a completely effective and safe treatment (Mojaverrostami et al., 2018). Due to the unavailability of medicine without side effects, there is an urgent need for alternative medicine for curing the symptoms of Multiple sclerosis. Herbals have potent antioxidant properties, anti-inflammatory, rejuvenating, antidiabet ,ant -cancerous and immune-modulatory properties with negligible side effects. Due to all these aspects, herba –based medicines are becoming more popular among the people. Also serving as a better alternative to the pre-existing drugs,with effective role in treating MS.(Wardhan et al., 2021)

Apossible pathogenic mechanism in the brain has been already appointed as syncytin-1 overexpression in astrocytes results in production of cytokines and reactive oxygen species followed by in vitro and in vivo oligodendrocyte injur(Antony et al., 2004)

Syncytin-1 is an envelope protein of thehuman endogenous retroviruses (HERVs) HERV-W family that is encoded by ERVWE1 locus located on chromosome 7q21.2. It is a cell–cell fusion glycoprotein expressed on the cell membrane forming a heterodimer, with a surface (SU) subunit and a transmembrane subunit (TM). (Montojo et al., 2020)

II. .METHODOLOGY

2.1. Protein Identification:

From the RCSB Protein Data Bank (PDB) acquired the Syncytin-1 protein(https://www.rcsb.org/structure/6RX1)The selected protein structure is downloaded from PDB in pdb format. The protein resolution is 2.10 Å with id number 6RX1. This protein data base is discovered in 1971, which is the hub of protein databases globally.

2.2. Ligand Preparation

The compoundsfor our work has been selected from review of literature.All the selected ligands were downloaded from the PubChem.(https://pubchem.ncbi.nlm.nih.gov) in .sdf format with 3D conformations. Nitroimidazole, Benzimidazole, Lidamycin and Quinoline are the compounds for which analysed wasperformed.PubChem is the huge public chemical database in globally. The PubChem. provided all the detailed information about the structure.After downloading the compounds in the .sdf format, the ligand file was converted

into .pdb format for performing the further analysis.The conversion process was done by online server SMILES translator.(https://cactus.nci.nih.gov/translate/)

2.3. Virtual screening

PyRx is the software which is used for screening the complex and finding the most compatibleThe virtual screening isdone by the help of PyRx. It determines the ligands binding ligand to docked with the target protein.Firstly,load the protein (Syncytin-1) in.pdb formatin the graphical window of the PyRx software. After loading convert into .pdbqt by making it into macromolecule.Then load the ligands one by one in the .sdf format by choosing specifically chemical sdf.Minimiseallthe ligands and then converted all them into the into the.pdbqt format and find the PyRx result which showsthe binding affinity with protein and ligands.Programme run on the PyRx also provide the Upper bound and lower bound RMSD values with E values.All the binding affinity was given in negative and for proceeding lowest binding energy compound was chosen.

2.4. Drug Likeliness Property Analysis

Through Swiss ADME we find out the drug likeliness property of the selected ligands, because of Lipinski's Rule of five. This determines the Lipinski rule properties in the ligands. The Lipinski's Rule of five is given below.

1.Hydrogen bond acceptors(HBA) shall be less than 10
2.Molecular weight of the ligands shall be less than 500 dalton.
3.Hydrogen bond donors(HBD) shall be less than 5
4.Partition co-efficient LogP shall be less than 5
5.Violations shall be zero or one but not more than 1

Now, firstly copy the compounds are selected which fulfil the Lipinski's Rule of five for a molecular docking. For checking the drug propertyCANINICAL SMILES code from pubchem of each and every selected ligands then paste in to Swiss ADME(http://www.swissadme.ch)and check the drug likeliness property.
Docking through AutoDock Vina using Mgl tool

Now, the protein (Syncytin-1) is loaded on the graphical window in pdb format. then delete the water molecules,add the hydrogen after doing this add theKollman charges, finally savethe file of protein molecule in .pdbqt format and similarly do in the case of ligand and conversion in pdb to pdbqt format. And then, generated the grid file and give the file name (grid). Txt format. At last, commands prompt (Cmd) was used for the resultsof AutodockVina using Mgl tooland the result file (output) was saved in the .pdbqt format.

2.5. Structural Visualization through PyMOL

To visualise the result of auto dockvina we use the PyMOL software. In the PyMOL we visualisedinteraction between protein and ligand. Firstly,loaded the protein in the pdbqt

format after this load the output file on the graphical window of the PyMOL in the pdbqt format and then visualised the binding affinity of protein with the ligand.

III. RESULT AND DISCUSSION

The targeted protein wasSyncytin-1**(figure:1)**which is also known as enverin.It is found in humans and other primates that is encoded by the ERVW-1 gene (endogenous retrovirus group W envelope member 1). Syncytin-1 is a cell-cell fusion protein whose function is best characterized in placentaldevelopment.(Dupressoir, L. C, et al.,2012, Soygur B, et al., 2016). This protein is responsible for causing the Multiple scleriosis(MS) in the population which affects the neural proper functioning in the affectded individuals.

Syncytin-1 shares many structural elements with class I retroviral glycoproteinsi.e. Murine Leukemia Virus gp, and HIV gp120, gp41). It has two subunit such as surface subunit (SU) and transmembrane subunit (TM), separated by a furin cleavagesite.(Cheynet V et al., 2005)

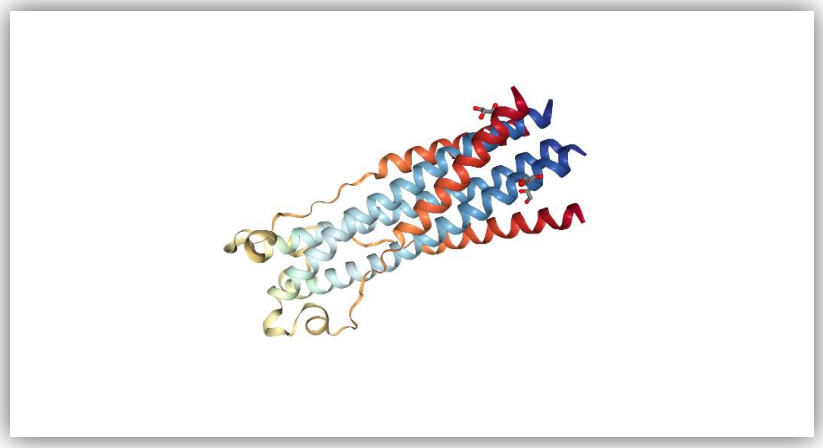


Figure 1 : 6RX1 Protein 3D structure(doi:10.1093/bioinformatics/bty419)

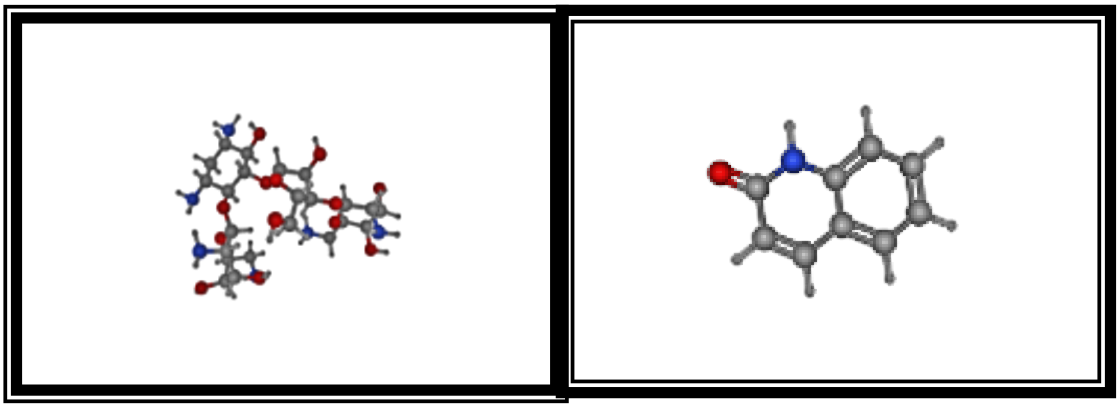
- **Classification:** Membrane protein
- **Organism(s):** Homo sapiens
- **Expression System:** Escherichia coli BL21(DE3)
- **Mutation(s)**: No

The protein Synctin 1 i.e., 6rx1 was donloaded from Protein Data Bank (PDB) in .sdf format and then saved into the folder.The selected ligands for targeting this membrane protein, all the selected ligands are shown in **figure: 2,**Lidamycin (62403), Quinoline (6038), Nitroimidazole (10701) and Benzimidazole (5798) were downloadedin .sdf and converted into the .pdb format by the help of SMILES converter online server and compounds with their detail information are given below in **table: 1.**

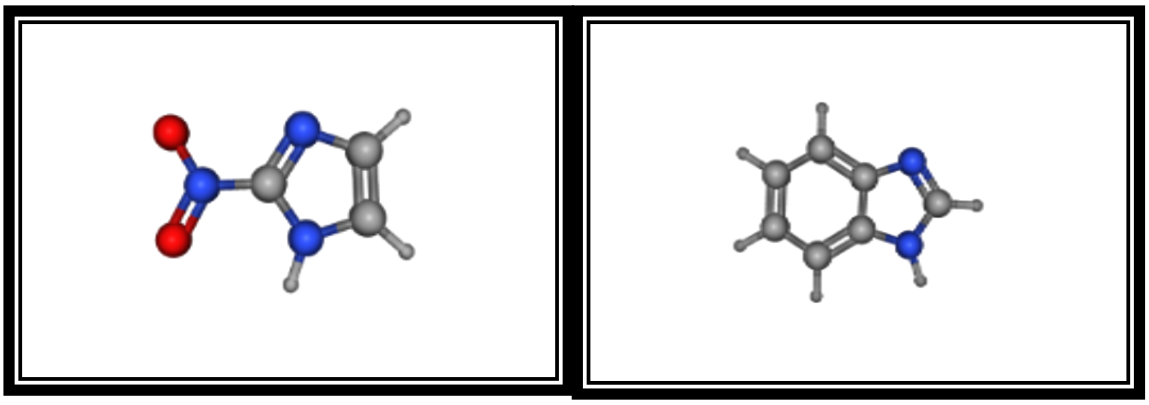
Table: 1. Compounds with their detailed information.

LIGAND NAME	PCID	MOLECULAR FORMULA	MOECULAR WEIGHT
Lidamycin(Neobiotic)	62403	$C_{23}H_{48}N_6O_{17}S$	712.7g/mol
Quinoline	6038	C_9H_7NO	145.16g/mol
Nitroimidazole	10701	$C_3H_3N_3O_2$	113.08g/mol
Benzimidazole	5798	$C_7H_6N_2$	118.14g/mol

Figure: 2- Three- Dimensional structures of the Natural Compounds



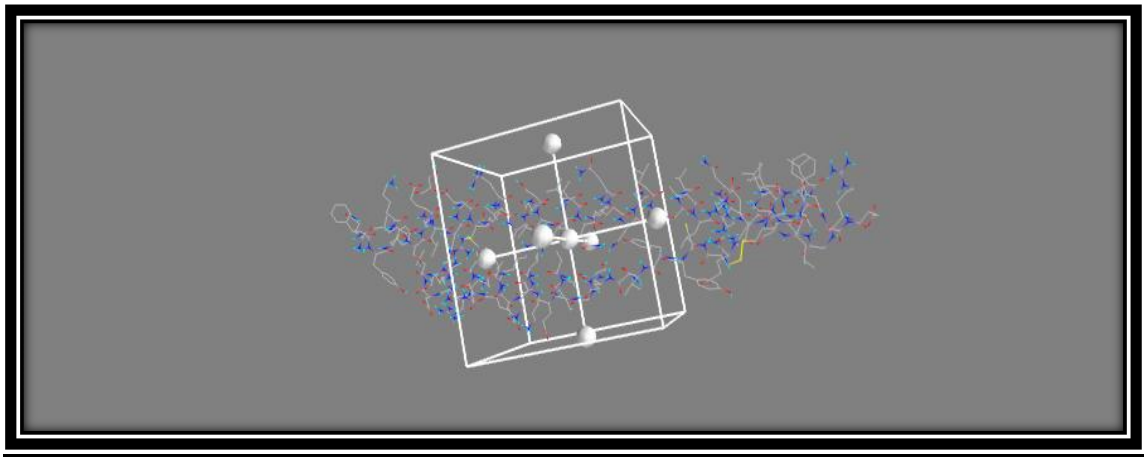
a). LIDAMYCIN b). QUINOLINE



c). NITROIMIDAZOLE d). BENZIMIDAZOLE

PyRx software helped in finding out the binding affinity of the molecules with the ligands.In PyRx software initially protein was loaded and converted into the .pdbqt file, then all the four ligands were also converted.The software provides the binding affinity of compounds.Grid box was also preparedby adjusting the x, y, and z coordinated.The picture is showing the grid box prepared by PyRx in **figure :3**

Figure:3 - Grid Box preparation in PyRx



According to the PyRx :

- The binding affinityof the Lidamycin was -5.6 with 783.48 E value according the resykt of PyRx software .
- The bindingaffinityofsecond compound Quinoline was -5.0, with 92.88 E value.
- The binding affinity ofthird compoundNitroimidazole was -4.0 with 2278.18 E value.
- The binding affinity of Fourth compoundBenzimidazole was -4.2 with 292.40 E value.

The given below **table:2** has shown the predicted values of Binding energy in negative, the lowest the value of the binding affinity, stronger the chances of the ligand toget bind with the protein easily.In this result, Lidamycin was showing the lowest value of binding energy in comparison to the other three compounds, Quinoline, Nitroimidazole and Benzimadzole compound.Based on this result of PyRx, the molecules were moved further for ADME profiling by the SwissADME online server.

SwissADME predicts the properties of the compound with different information regarding the Hydrogen donor, acceptor, molecular formula, iLogp values, molecular weight and so on.SwissADME translates the CANONICALSMILES copied from the PubChem. CANONICALSMILES of the compounds helps in Knowing the Drug proeperties by SwissADME.SwissADME follows the Lipinski rule of five, based on.This compounds are selected for acting as a drug.

Table; 2 PyRx result with Binding energies of all the phytochemicals

LIGANDS NAME	PCID	E VALUE	BINDING ENERGY
Lidamycin(Neobiotic)	62404	783.48	-5.6
Quinoline	6038	92.88	-5.0
Nitroimidazole	10701	228.18	-4.0
Benzimidazole	5798	292.40	-4.2

The drug likeliness property of all the four ligand moecules waspredicted, whether they follows theLipinski rule of five or not.The binding affinity of the Lidamycin was the lowest affinity based on the above mentioned result by PyRx. But, according the computed result of SwissADME shown in **table: 3**,it doesnot follows the Lipinski rule of five. It consist of 3 violations due to which it was not selected for the docking or cannot be used as a drug. Next, the Quinoline (PCID 6038) compound with -5.0 binding energy was selected and it shows that it follows the Lipinski rule of five with zero violations in it. Similary, other two compounds were selected for the checking pf properties and these two natural compound Nitroimidazole (PCID 10701), Benzimadzole (PCID 5798) also follows the Lipinski rule of five with zero violations.

These three compounds which has shown that they follows the rule of five can be selected for docking with the protein finally. The**table:4**is showing the Drug likeliness property of the four compounds with number of violations in it.

Table :3 -The binding energy of the ADME approved compound shown below with their PubChem. Id

Ligandmolecules	Bindingenergy
6978	-5.0
10701	-4.0
5798	-4.2

TABLE:4Drug likeliness property analysis

Compound Name	Molecularweight	H-bondDonor	H-bondAcceptor	Partitionco-efficientMlogP	Violation
Lidamycin	712.72g/mol	15	23	0.59	No;3 violations
Quinoline	145.16g/mol	1	1	1.56	Yes: 0 Violation
Nitroimidazole	113.07 g/mol	1	3	0.21	Yes; 0Violation
Benzimadazole	118.14 g/mol	1	1	0.90	Yes;0 Violation

Finally the proteinSynctin 1, 6rx1 was docked with the lowest binding affinity compound and the compound which followed the Rule of five was selected for preceeding.The compound Quinoline has passed both the criteria and docked with the 6rx1 protein structure.

AutoDock software, was used for molecular docking with the selected ligands.In the graphical window of the AutoDock are shown in **figure:4**, the protein 6rx1 was uploaded.Then allthe water molecules were deleted for the work. Then polar hydrogen bonds were added into it by following addition of Kollman charges.The .pdb file of Syncytin-1 proetin was used for initial steps.

Then, by converting the same protein file into .pdbqt format was saved into the preferred folder.Afterwards, ligand Quinoline .pdb file was uploaded and converted into .pdbqt file as well by giving the recognizable name for ligand file.Byagain loading the protein 6rx1 in the same window grid box was prepared with 40, 40and 40 , x,y, z coordinates values.

The grid box parameters was setted properly and config. Txt file was saved.After performing all the coversions and saving the data, command prompt (cmd) was opened.Command prompt analysed the docking score of the protein synctin- 1 (6rx1) and the ligand Quinoline in nine different modes values with RMSD UB and RMSD LB values are given in **table: 5**After that, the output file and target protein was visualized into the PyMol visulaization tool.

Figure: 4. AutoDock window with 6rx1 loaded protein after removal of water molecules

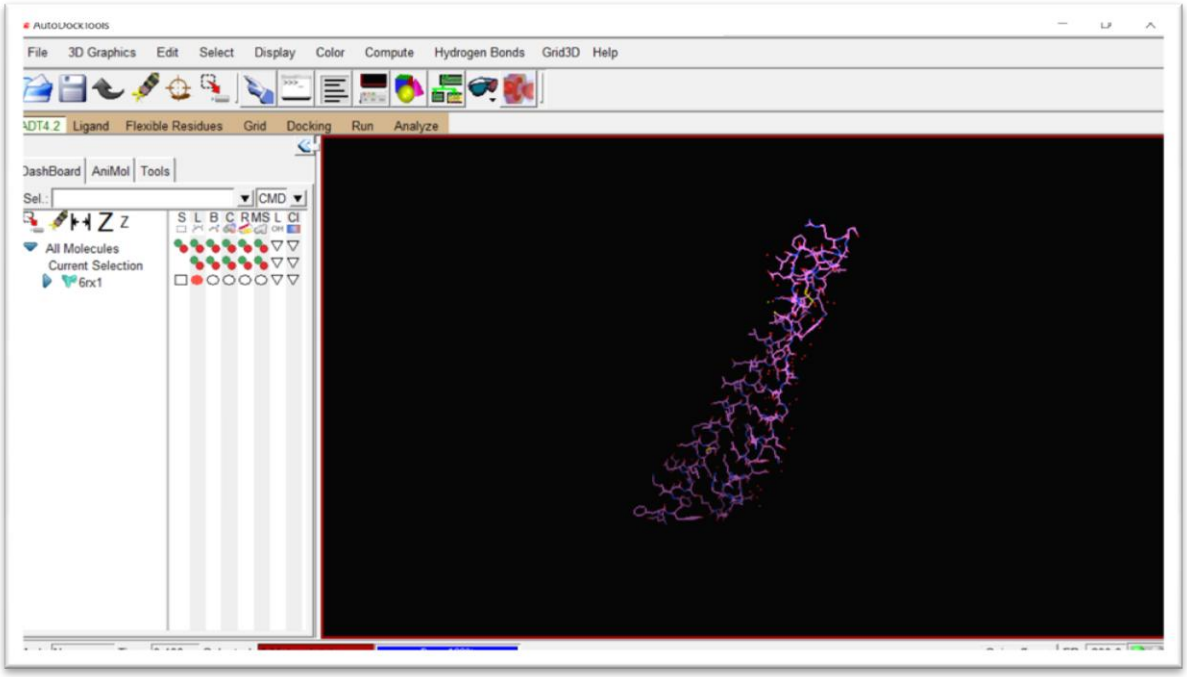
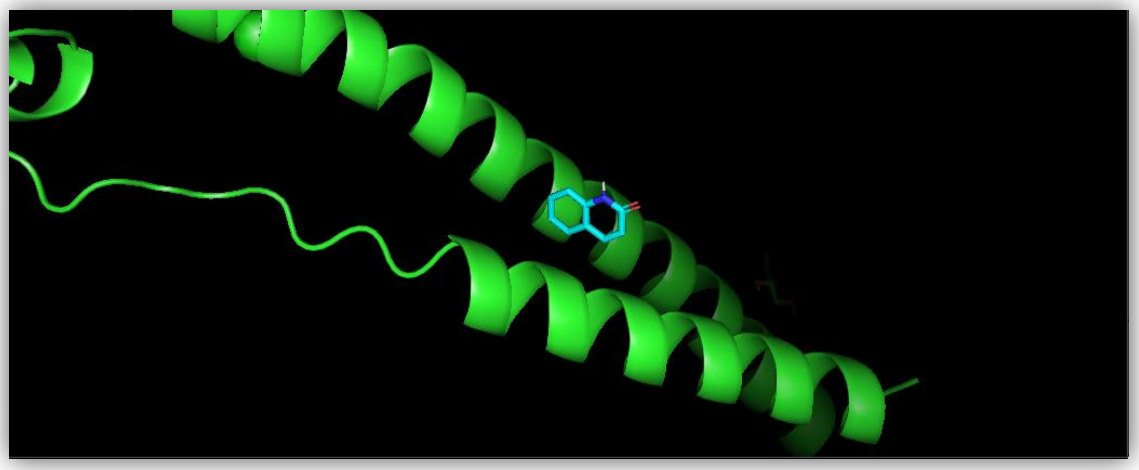


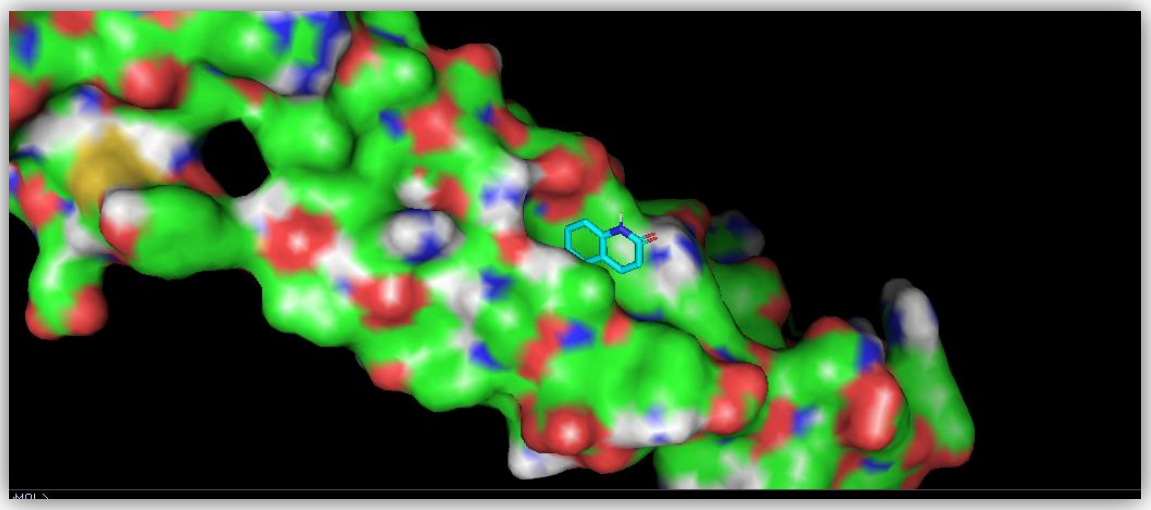
Table: 5 - Autodock Table

Mode	Binding Affinity[kcal/mol]	Distance from best mode	
		RMSD lower bound	RSMD upper bound
1	-4.9	0	0
2	-4.8	1.250	2.149
3	-4.7	1.899	2.506
4	-4.6	2.184	3.875
5	-4.5	18.268	20.047
6	-4.4	10.968	12.398
7	-4.4	17.758	19.536
8	-4.2	9.753	10.968
9	-4.2	1.066	2.391

At the end, the PyMOL was used to visualize the structure of the protein(syncytin) and the selected molecule (quinoline). In this software the binding between the protein and the ligand were show the best binding affinity with the protein.



(a) The structure of the binding SYNCYTIN 1 with QUINOLINE



(b).Show the structureof the binding SYNCYTIN1 with QUINOLINE molecules by selecting the option “molecular surface”

Figure : 5 -Binding between the protein synctyin 1 and ligand quinoline.

IV. CONCLUSION

Medicinal plants have opened a new horizon in curing neurodegenerative disorders such as Parkinson's disease, AD and multiple sclerosis with reduction in their adverse effects. Literature data reviewed for this study has been indicated that herbal medicines could be effective in the treatment of MSdisease by reducing the demyelination, improving remyelination and suppressing the inflammation in the CNS. On the basis of the docking result, Quinoline natural compoundcould be considered as the future candidate which can be used for developing the noval drug for targeting MS disease. Out offour compounds, Lidamycin, Quinoline, Nitriomadazole and Benzimidazole compounds, Quinoline compound has shown potency to act against the syncytin 1 protein, and also has the potential to act as drug. Based on this preliminary study,the herbal compounds can be used for treating and maintaning the health related problems.

V. ACKNOWLEDGEMENTS

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VI. CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

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