ejpmr, 2021,8(8), 483-487.

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

STUDY THE EFFECT OF QUERCETIN AGAINST SORTILIN-RELATED RECEPTOR TO CURE ALZHEIMER'S DISEASE

Km. Radha[1], Niketa Singh[1], Khushboo Rana[1], NoopurKhare[2,3] and Abhimanyu Kumar Jha[1,2]*

[1]Department of Biotechnology, Faculty of Life Science, Institute of Applied Medicine and Research, Ghaziabad, Uttar Pradesh, India.

[2]Institute of Technology and Management, Meerut, Uttar Pradesh, Affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

[3]Shri Ramswroop Memorial University, Barabanki, Uttar Pradesh, India

***Corresponding Author: Abhimanyu Kumar Jha**

Department of Biotechnology, Faculty of Life Science, Institute of Applied Medicine and Research, Ghaziabad, Uttar Pradesh, India.

Article Received on 30/05/2021 **Article Revised on 21/06/2021** **Article Accepted on 11/07/2021**

ABSTRACT

Alzheimer's disease [AD] is one of the most common types of Neurodegenerative disease in worldwide. It is the most common type of disease which causes dementia in the elderly. The molecular docking technique is used for observing the interaction between ligands and a target protein-making drug. Molecular docking has a vital role in drug discovery. So, this technique plays a vital role for screening the natural compounds with target protein, it depends upon binding energies. The molecular docking is helps in investigates the expression of SOR1 protein with natural compound Quercetin for the prepration of drug to treat Alzheimer's disease In 1906, Dr. Alos Alzheimer's noticed that the changes in the tissue of the brain in a "woman" who had died of a usual mental illness. Dr. Alos Alzheimer's gives their named Alzheimer's disease. Molecular docking has become an increasingly important tool for drug discovery. The PDB was recognized in the year 1971 for all protein data collected in a particular platform, which is the universal platform of biological protein structural data.

KEYWORDS: Auto Dock Vina, AD, SOR1, Ligand and Molecular docking.

INTRODUCTION

Alzheimer's disease is a neurological disorder that is associated with cognitive decline which causes to shrink the brain and allow brain cells to die.[1] It is the most common type of disease which causes dementia in the elderly. Memory loss symptom occurs in the Alzheimer's disease. In 1906, Dr. Alos Alzheimer's noticed that the changes in the tissue of the brain in a "woman" who had died of a usual mental illness. Dr. Alos Alzheimer's gives their named Alzheimer's disease.[2] As of 2015, there were approximately 29.8 million people worldwide with AD,[3] with about 50 million of all forms of dementia as of 2020.[4]

Sortilin-related receptor" (SORL1 is called LR11 or SORLA) encoded a hybrid receptor with their multiple types of domains due to interacting the intracellular sorting and trafficking of proteins into their significantly subcellular compartments. These membrane-bound receptors are involved in the endosome sorting of protein between the plasma membrane, endosomes, and trans-Golgi network.[5,6]

Molecular docking has become an increasingly important tool for drug discovery. The molecular docking was used to observe the interaction between the target protein and compounds. Natural products have been used for the treatment of various diseases and are becoming an important research area for drug discovery. Benzimidazile, Lidamycin, Quinolone, Quercetin and Rutin all natural compounds were selected for the drug prepration of Alzheimer's disease.

MATERIALS ANDMETHODS

Identificationofprotein

The structure of protein [Sortilin-related receptor (PDB ID: 3G2S)] which used in docking download from the Uniprot [RCSB (Protein Data Bank)].[7-8] Protein structure was downloaded in ".pdb" format for docking prcoess.

The PDB was recognized in the year 1971 for all protein data collected in a particular platform, which is the universal platform of biological protein structural data. It was established by "Brookhaven National Laboratories".[9] In the "Uniprot" all protein data are found in one platform.

Identification of Ligands

Benzimidazile, Lidamycin, Quinolone, Quercetin and

Rutin all natural compounds were selected for the drug prepration of Alzheimer's disease. All the natural compounds downloaded from the online server PubChem (https://pubchem.ncbi.nlm.nih.gov/),[10-11] in ".sdf" format with 3D structure. Then all compounds convert from ".sdf" into ".pdb" format by online SMILES Translator.[11] These ".pdb" files were used for further tools and software's.

Virtualscreeningthroughpyrx

Screening of ligands was used above files through PyRx software. This software was used to screening the ligands molecules with minimum binding energy and protein target. Those ligands having minimum binding energy analyzed by the online sever drug likeliness property for further process Autodock.

- PyRx starts with firslty loading of protein molecule, in ".pdb" format and then saved into ". pdbqt" format .
- Then all the ligands were imported in .sdf format in PyRx window.
- All ligands convert from .sdf file to ". pdbqt" file.
- Docking was performed to show the interaction between protein target and ligand molecule.
- Bindingenergy ofligandsscreened and select only minimum energy of ligands.

Druglikelinesspropertyanalysis

Drug likeliness property was analyzed through Swiss ADME. The screened ligands were analyzed for observation of its drug property. Copy the notation CANONICAL SMILE from the online server Pubchem and it pasted on the Swiss ADME. Ligand analyzed by Lipinski rule of five for drug preparation. Lipinski rule of five states the following points:-

1. Molecular weight (MW) = Not more than 500 Dalton.
2. Hydrogen bond donors (HBD) = Not more than 5 (< 5).
3. Hydrogen bond acceptors (HBA) = Not more than 10 (< 10).
4. Partition co-efficient (MLogP) = Not more than 5 (< 5).
5. Violation (Lipinski) = Not more than 1.

Docking Through Autodock Vina

1. Load targeted protein which is in .pdb format.
2. Delete water molecules from protein.
3. Adding hydrogen polar atoms in target protein.
4. Adding Kollman charges in the protein molecule and then the target protein saved in ". pdbqt" format in a specific folder.
5. Ligand molecule was load in .pdb format and then the ligand molecule convert into ". pdbqt" format in specific folder.
6. Then select the grid box for final docking.
7. Using command prompt (cmd) for the final docking and for final result analysis .

Structure Visualization Through Pymol

Structure of protein was visualization by the using of the tool PyMOL 2.4. PyMOL 2.4 was freely available on online.

- The target protein in ".pdbqt" format was loaded on PyMOL 2.4.
- Then the "output.pdbqt" result comes from cmd load in PyMOL for visualization of final protein structure with compound.
- The final structure of targeted protein with the ligand molecule by select the option molecular surface in "shown as" option.

RESULTS AND DISCUSSION

The crystal structure of Homo sapiens Sortilin-related receptor in ".pdb" format was downloaded from Uniprot (PDB) as shown in Figure 1 and biological assembly structure Figure 2 Sortilin-related receptor. Sortilin-related receptor belongs to Protein Transport class with resolution of protein was 1.70 Å and method was X-ray diffraction. The structures of all ligands which used for drug preparation were downloaded in ".sdf" from the Pubchem Online server and also download the 2D or3-D structure from Pubchem as shown in Figure 3 (a), (b), (c), (d) and Figure 4(a), (b), (c) and Table 1.

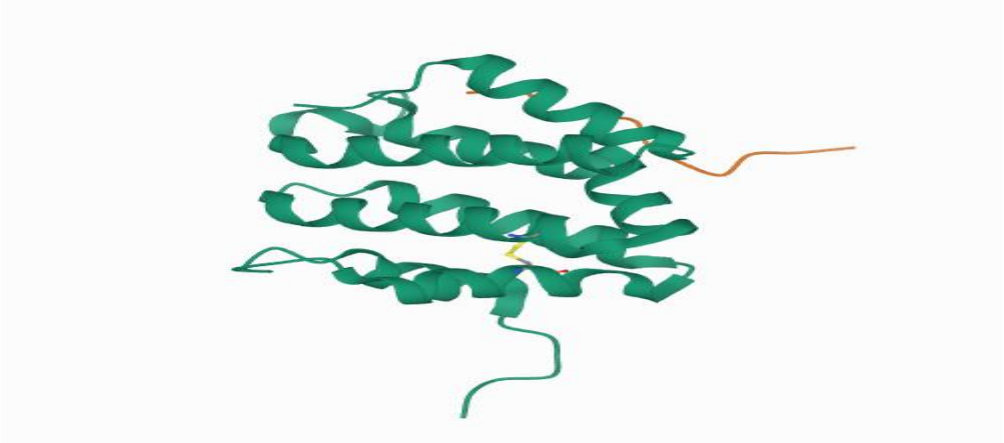
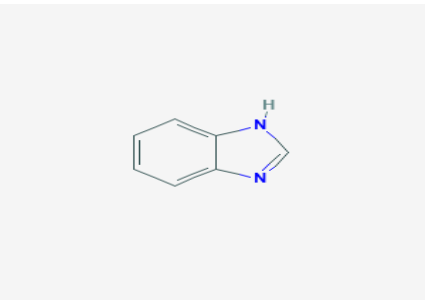
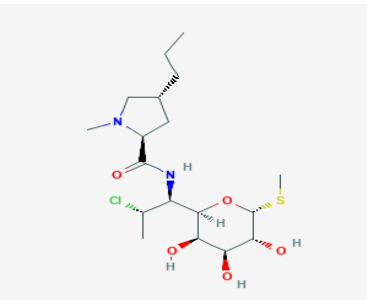


Figure 1: Biological assembly structure of Protein [PDB: 3G2S].

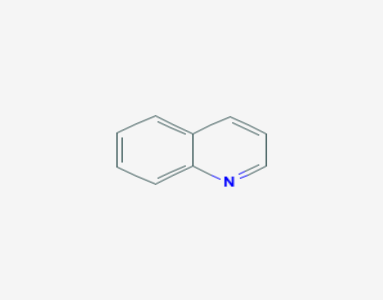
PROTEIN	**:**	**SORTILIN RELATED PROTEIN**
GENE	**:**	**SOR1**
PDB ID	**:**	**3G2S**
ORGANISM	**:**	**HOMO SAPIENS**
MUTATION	**:**	**NO**
RESOLUTION POWER	**:**	**1.70Å**
RESOLUTION FREE VALUE	**:**	**0.226**
RESOLUTION WORK VALUE	**:**	**0.196**
RESOLUTION OBSERVED VALUE	**:**	**0.197**
METHOD OF PROTEIN DOWNLOAD	**:**	**X-RAY DIFFRACTION**



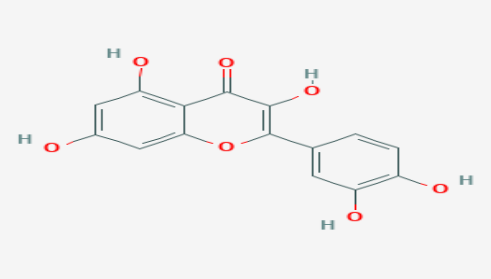
BENZIMIDAZILE
CID – 5798
MW – 118.136 g/mol
MF – C7H6N2



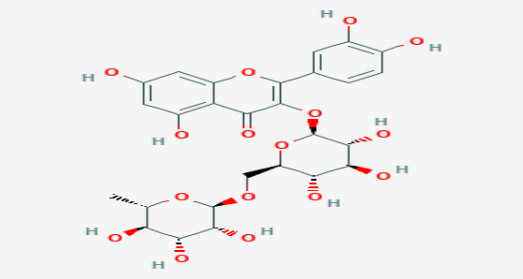
LIDAMYCIN
CID – 62404
MW – 614.644 g/mol
MF – C23H46N6O13



QUINOLONE
CID – 6038
MW – 145.158 g/mol
MF – C9H7NO



QUERCETIN
CID – 5280343
MW – 302.236 g/mol
MF – C15H10O7



RUTIN
CID – 5280805
MW – 610.518 g/mol
MF – C27H30O16

Figure 2: 3D structure of Benzimidazile, Lidamycin, Quinolone, Quercetin and Rutin.

The ligand molecules Virtual screening was done through PyRx software within minimum binding affinity of ligands were screened. The binding affinity of Benzimidazile was -5.4, Lidamycin was -5.8, Quinolone was -6.7, Quercetin was -8.5 and Rutin was –7.2 as shown in Table 1, 2 and 3. The ligands which were selected after PyRx result were Quinolone, Quercetin and Rutin and further analyzed for drug likeliness property analysis.

Table 1: Result of Compounds and target Protein by PyRx.

Compound	Ligand	Binding Affinity	Mode	RMSD lower Bound	RMSD upper Bound
Benzimidazile	**SOR1_5798_mmff94_E = 9.22**	**-5.4**	**0**	**0**	**0**
		-5.2	**1**	**14.742**	**16.078**
Lidamycin	**SOR1_62404_mmff94_E = 381.88**	**-5.8**	**0**	**0**	**0**
		-5.3	**1**	**1.447**	**1.959**
Quinolone	**SOR1_6038_mmff94_E = 0.61**	**-6.7**	**0**	**0**	**0**
		-6.2	**1**	**12.419**	**13.712**
Quercetin	**SOR1_5280343_mmff94_E = 55.86**	**-8.5**	**0**	**0**	**0**
		-8.4	**1**	**1.663**	**2.271**
Rutin	**SOR1_5280805_mmff94_E = 254.99**	**-7.2**	**0**	**0**	**0**
		-5.5	**1**	**4.265**	**9.436**

Table 2: Result of SWISS ADME based upon Drug Likeliness Property Analysis.

Compounds Name	Binding Affinities	Molecular Weight	H-Bond Acceptor	H-Bond Donor	MLOGP	Lipinski Violation
Benzimidazile	-5.4	118.14g/mol	1	1	0.98	Yes, 0 violation
Lidamycin	-5.8	712.729g/mol	23	15	-8.28	No, 3 violation
Quinolone	-6.7	145.16g/mol	1	1	1.65	Yes, 0 violation
Quercetin	-8.5	302.24g/mol	7	5	-0.56	Yes, 0 violation
Rutin	-7.2	610.52g/mol	16	10	-3.89	No, 3 violation

The protein target SOR1 (PDB ID: 3G2S) and Quercetin (CID: 5280343) were docked byAutoDockVina software. The interaction was visualized by PyMolafter 9 poses of AutodockVina result as shown in table 4 via figure 3.

Table 3: Binding Energies of different Ligands.

Sr.no.	Compound	Binding Affinity	CID
1.	Quinolone	-6.7	6038
2.	Quercetin	-8.5	5280343
3.	Rutin	-7.2	5280805

Drug likeliness property analysis was performed by SwissADME and ligands were selected according to Lipinski's Rule of Five as shown in Table 2. Quercetin was a ligand that qualifying all the properties of Drug.

Table 4: Autodock Vina Result

Mode	Affinity (kcal/mol)	Dist. From best mode	
		RSMD L.B	RSMD U.B
1.	-8.5	0.000	0.000
2.	-8.5	17.25	17.88
3.	-8.5	17.696	18.623
4.	-8.4	1.647	2.263
5.	-8.4	17.98	18.79
6.	-8.0	1.729	6.990
7.	-7.9	1.256	6.519
8.	-7.8	16.736	19.721
9.	-7.5	15.697	18.506

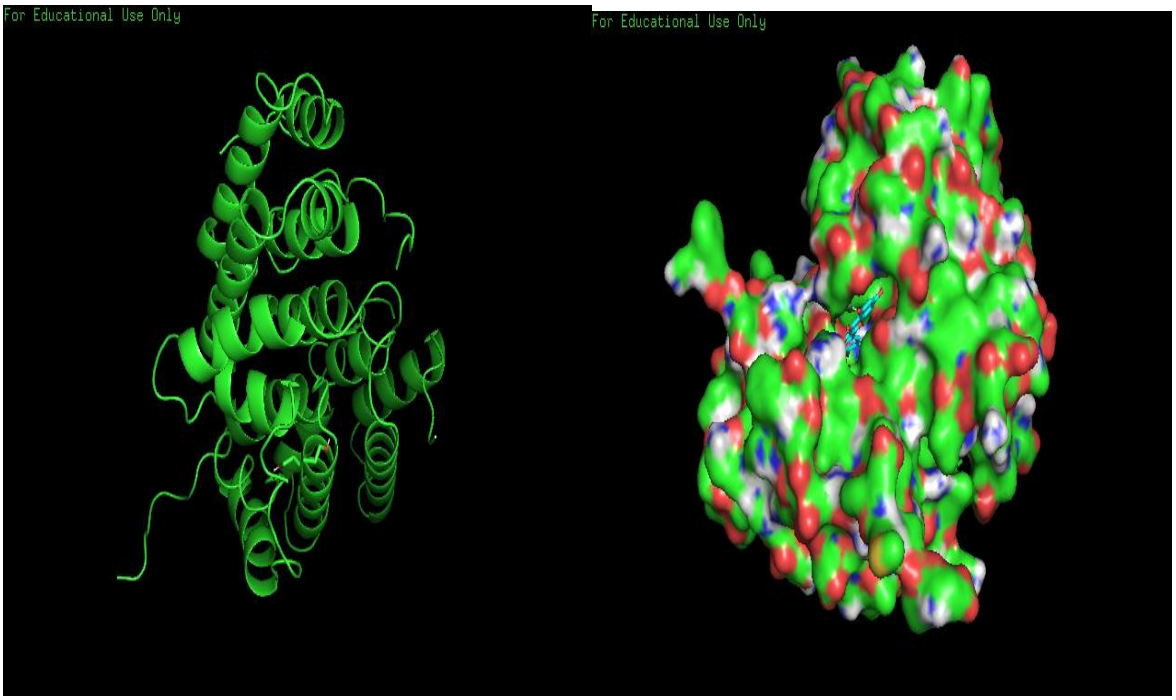


Figure 3: Interaction of SOR1 (PDB ID: 3G2S) with Quercetin (CID: 5280343)

CONCLUSION

The molecular docking is a type of technique which wasinvestigates their potential value of natural compound (ligand) against the selected protein (receptor/target). According molecular docking, interaction of the ligand (Benzimidazile, Lidamycin, Quinolone, Quercetin and Rutin) with the target protein SOR1 (PDB ID: 3G2S). Thus, Quercetin was taken from natural sources which can use as drug for the treatment of Alzheimer's disease.

ACKNOWLEDGEMENT

The authors acknowledge the help provided by Department of Biotechnology, Faculty of Life sciences, Institute of Applied Medicines and Research, Ghaziabad, India.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

1. R. A. Armstrong, "A critical analysis of the 'amyloid cascade hypothesis'," *Folia Neuropathologica*, 2014; 52: 3: 211–225.
2. Blennow K, de Leon MJ, Zetterberg H Alzheimer's disease. Lancet, 2006; 368: 387–403.
3. Hardy J, Selkoe DJ The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science, 2002; 297: 353–356.
4. GBD 2015 Disease Injury Incidence Prevalence Collaborators (October). "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015". Lancet, 2016; 388(10053): 1545–1602. doi:10.1016/S0140-6736(16)31678-6. PMC 5055577. PMID 27733282.
5. Wilson CM, Naves T, Saada S, Pinet S, Vincent F, Lalloué F, Jauberteau MO. The implications of sortilin/vps10p domain receptors in neurological and human diseases. *CNS Neurol Disord Drug Targets*, 2014.
6. Caroline Horvath AJ, GaelleBouletAV, VirginieRenoux M,Philippe Delvenne O, John-Paul JB.Mechanisms of cellentry by human papillomaviruses: anoverview.VirolJ, 2010; 7: 11.
7. SureshkumarP,SenthilrajaO,KalavathyS.Insilicodockinganalysisof Calotropisgigantean(l.)R.BRderivedcompoundagainstanti-cervicalactivity.BioinfoPublication, 2012; 1(1); 9-12
8. Graff,J.&Mansuy,I.M.Epigeneticcodesincognitionandbehaviour.Behaviouralbrainresearch192,70:87,https://doi.org /10.1 016/j.bbr.2008.01.021, 2008.
9. Kim,S.,Thiessen,P.A.,Bolton,E.E.,Chen,J.,Fu,G.,Gindulyte,A.,…Bryant,S.H.(2015).PubChemSubstanceandCompounddatabases.NucleicAcids.
10. https://cactus.nci.nih.gov/translate/.
11. https://cactus.nci.nih.gov/cgi-bin/translate.tcl.