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Molecular Docking Study on the Effect on Lamin – B1 through Compounds for the Treatment of Multiple Sclerosis

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Abstract: ***Multiple sclerosis (MS) is a demyelinating disease that can disrupt or damage various parts of our body i.e. nerve cells, brain and spinal cord, etc. The damaged cells of the body can disrupt the ability of the the nervous system to transmit signals for the functioning of the body. MS may result in double vision, blindness in one eye, muscle weakness and trouble with coordination and sensation. This disease is a long-term disease that may not be cured rapidly and easily. MS may be found at an age of 20-50.***
Lamin B1 is a protein that is found in humans. A gene i.e LMB1 encodes for this protein. The nuclear lamina consists of a 2D matrix of protein which locates next to the inner nuclear membrane.
Molecular docking is a virtual or e tool that promotes the drug designing technique in a computerized way or called computer-assisted Drug Designing [CADD]. This can be used to complete the goal of docking is to see the binding of the protein and ligands In our study, one of the naturally occurring products was used for Multiple sclerosis treatment i.e Quercetin .
The Quercetin ligand molecule gives a promising way of making the drug against the Multiple Sclerosis disease. According to this study, Quercetin may be used as a drug agent against Multiple Sclerosis disease in the future.
Keywords: Multiple Sclerosis, Lamin –B1, Quercetin, Molecular Docking, LMB1, CADD.

I. INTRODUCTION

Multiple sclerosis (MS) is a disease which may damage various parts of our body. [1] The disease may show symptoms like damaging up of the cells in the body which may disrupt the ability of the nervous system to transmit signal for the functioning of our body. [4,6,7]. The common symptoms of this disease are double vision, blindness in one eye, muscle weakness and trouble with coordination and sensation [1,8,9]. This disease is a long-term disease that may not be cured rapidly and easily. MS may be found as usual onset at the age of 20-50 [2]. MS can be treated by the medication as well as the physical therapy [1]. As a result the frequency of the MS disease in the year 2015 there were two million people which were affected due to MS and the death ratio was 18,900 in the year 2015 [5].

A. Various Sign And Symptoms Of The Multiple Sclerosis

1) Central:- Fatigue , Cognitive Impairment , Depression , Anxiety , Unstable mood .
2) Visual : - Nystagmus , Optic neuritis , Diplopia
3) Speech : Dysarthria
4) Throat : Dysphagia
5) Musculoskeletal :- Weakness , Spasms , Ataxia
6) Sensation : - Pain , Hypoesthesias , Paraesthesias ,
7) Bowel : - Incontinence , Diarrhea or Constipation
8) Urinary : - Incontinence , Frequency or Retention

Lamin B1 is a protein that is found in humans. A gene i.e LMB1 encodes for this protein [13,14,15]. The nuclear lamina consists of a 2D matrix of protein, which locates on next to the inner nuclear membrane. The Lamin family of the protein can makes the matrix that conserves evolution. The lamina matrix is reversibly disassembled as the protein of the lamina gets phosphorylated during the mitosis action.

The Lamin protein is involved in various actions i.e gene expression, Chromatin structure, and nuclear stability. It can be of two types consisting of the vertebrate Lamins, and the gene encodes 1 of the 2, B type protein i.e B1 [15]. Along with the heterochromatin, Lamin B is bind to the inner surface of the nuclear membrane onto the Lamin B receptor and into the nuclear membrane, a fibrous membrane can be found which can provide a framework for the nuclear envelope, and this can also found interaction with the chromatin [16].

Molecular docking is a virtual method that promotes the drug designing technique in a computerized way or called computer assisted Drug Designing [CADD]. This can be used to complete the goal of docking to see the binding of the protein and ligands, and give a view of both protein and ligands molecule, how favorable they are in binding, which helps Drug Designing easier. .The main objective of this study is to find the sites of the lamin b1 protein (i.e Domain and Active Sites, then by using molecular docking we accessed our selected molecules and determine their active sites, and can be used for further studies and the therapeutic agents –against the Lamin B1.

II. SELECTED MATERIAL AND THEIR METHODS

A. Identifying protein from Uniprot

The protein molecule i.e Lamin B1 was downloaded from UniProt. Uniprot database is a hub for protein information. The desired protein was downloaded in .pdb format file. The Protein Data Bank was recognized from the year 1971 which was established by "Brookhaven National Laboratories" [17].

B. Identifying ligands from Pubchem

Compounds were downloaded from Pubchem, it is also a freely available database. The selected natural compounds were downloaded from this Pubchem platform i.e *Phyltetralin, Quercetin, Ricinoleic Acid.* Compounds were downloaded in .sdf format file. Further, this .sdf file was converted into the .pdb format by the online sdf to pdb converter. [18].

C. Virtual Screening of Ligands Through PyRx

The protein molecule (Lamin B1) and ligand molecule (Phyltetralin, Quercetin, Ricinoleic Acid) were interacted with each other and their binding affinities were seen. The work was carried in PyRx software which showed the binding of protein and ligand. The protein molecule was loaded in .pdb format and the ligand molecules were loaded in .sdf format. The protein molecule and ligands were converted to .pdbqt format before docking.

D. Drug Likeness Analysis through Swiss ADME

The drug likeness property was checked for all the selected ligands through Lipinski's rule of five. Lipinski's rule of five enlist the following properties:-

1) The molecular weight of the ligands should not be more than 500 dalton.
2) The hydrogen bond donor (HBD) should not be more than 5.
3) The hydrogen bond acceptor (HBA) should not be more than 10.
4) The partition co –efficient (MLogP) should not be more than 5.
5) The violation (Lipinski) should not be more than 1 [19].

These measurements can be followed for making a good drug. For checking these values, the SMILES notations were copied fom Pubchem and were pasted in SwissADME. The final selection of the ligand molecule was done through SwissADME result.

E. Docking through the Mgl tool (Autodock Vina)

An Mgl tool is used for the final docking of the molecules through Autodock Vina. The protein molecule was uploaded in .pdb format and the water molecules were deleted by adding hydrogen, and the Kollman charges and finally the protein molecule was saved in .pdbqt format. The ligand molecule were uploaded in .pdb format and were saved in .pdbqt format. The grid box values were saved in grid.txt format. The config file was also generated by using grid values and was saved in .txt format and docking was performed.

F. Structure Visualization of Binding Molecules Through PyMol

PyMol 2.4 software is a freely available software. The structure of the binding protein and the ligand were visualized under PyMol software.

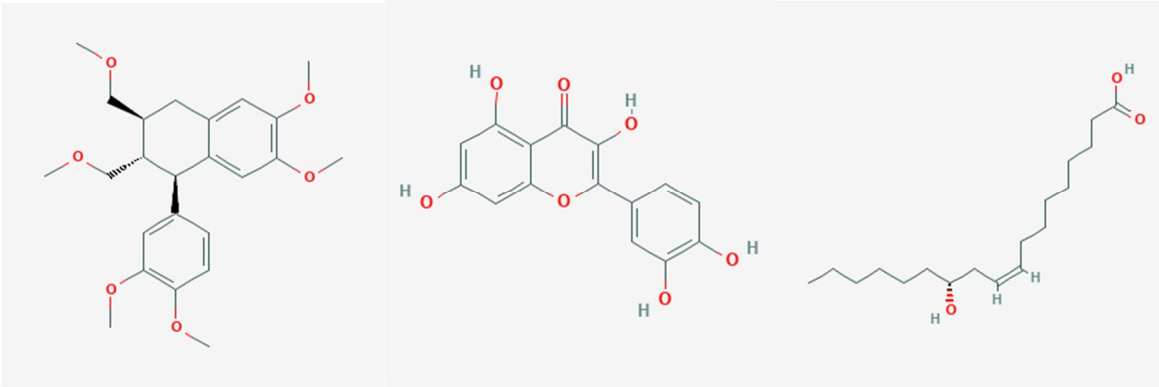
III. RESULT AND DISCUSSION

Human crystal structured protein Lamin-B1 were taken from the uniprot platform in the .pdb format. The details of protein are as follows:

1) Classification From : Structural Protein
2) Organism(s) From: Homo sapiens
3) Expression System From: *Escherichia coli* BL21(DE3)
4) Mutation(s) is : No
5) Method is : X-RAY DIFFRACTION
6) Resolution is : 2.39 Å
7) R-Value Free is : 0.245
8) R-Value Work is : 0.238
9) R-Value
10) Observed is : 0.238 **[20]**

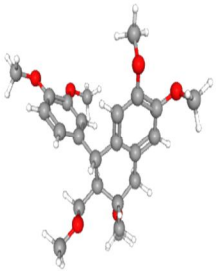
Figure 1: The Crystal structure of human Lamin-B1

The natural compounds were downloaded from the Pubchem platform. The 2D structure of ligands (Phyltetralin, Quercetin, Ricinoleic Acid) are shown in Figure 2 and 3D structure of ligands are in Figure 3. The compound were downloaded from Pubchem in .sdf format and finally were converted to .pdb format.

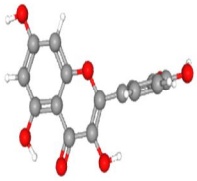


A. Phyltetralin B. Quercetin C. Ricinoleic Acid

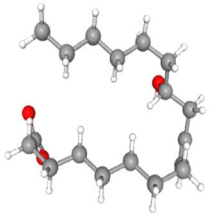
Figure 2: 2D structures of ligands



A. Phyltetralin



B. Quercetin



C. Ricinoleic Acid

Figure 3: 3D structures of the ligands.

Table 1. Details of ligand molecules.

S. No	Pubchem CID No.	Name of Ligands	Molecular Weight	Molecular formula	H.bond donar	H.bond acceptor	MLogP
1.	11223782	Phylteralin	416.51 g/mol	$C_{24}H_{32}O_6$	0	6	2.03
2.	5280343	Quercetin	302.24 g/mol	$C_{15}H_{10}O_7$	5	7	-0.56
3.	643684	Ricinoleic Acid	298.46 g/mol	$C_{18}H_{34}O_3$	2	3	3.69

IV. MOLECULAR DOCKING

PyRx software was used for the initial docking of the ligand molecule. PyRx gives result of ligand molecule in the aspects of Mode, rmsd upper bond , rmsd lower bond and the Binding Affinity with the Lamin-B1 protein molecule . The values of Mode , rmsd/ub and rmsd/lb of all three ligand (Phyltetralin , Quercetin and Ricinoleic Acid) is Zero (0) , but the Binding Affinity values are different (i.e -5 / -7.6 / -4.6). The Result of PyRx is listed below in table 2.

Table 2:

Ligand	Mode	Binding Affinity	rmsd/ub	rmsd /lb
Phyltetralin	0	-5	0	0
Quercetin	0	-7.6	0	0
Ricinoleic Acid	0	-4.6	0	0

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As by the PyRx, the results shows the minimum binding affinity in the sequence of -7.6 < -5.8 < -4.6 of Quercetin < Phyltetralin < Ricinoleic Acid. The druglikeliness property can analysed by the SwissADME online server. The final selected best suitable ligand molecule used for targeting the protein molecule was Quercetin. Quercetin was qualifying Lipinski's rule of five, and was used for the further Autodocking.
The resulting values are shown in Table 3.

Table 3: Analysis of SwissADME values.

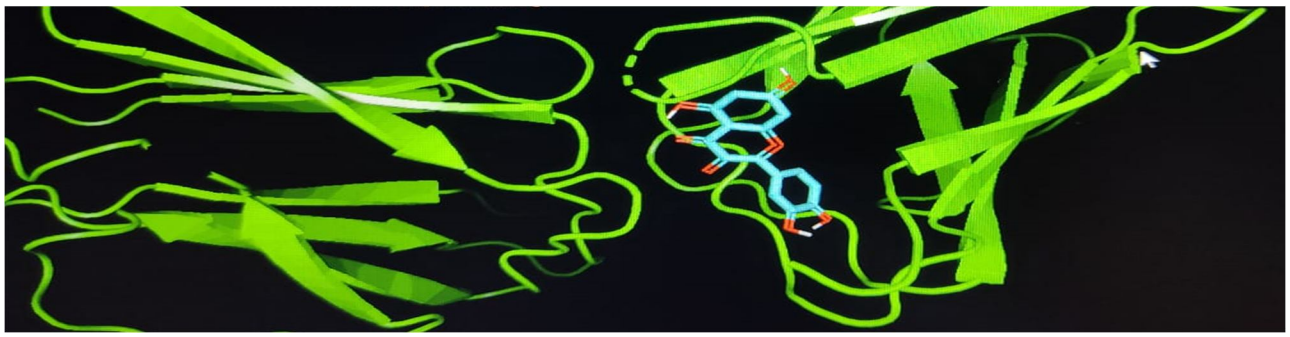
S. No	Name of Ligands	Molecular Weight	H.bond donar	H.bond acceptor	MLogP	Lipinski
1.	Phylteralin	416.51 g/mol	0	6	2.03	Yes ; 0 violation
2.	Quercetin	302.24 g/mol	5	7	-0.56	Yes ; 0 violation
3.	Ricinoleic Acid	298.46 g/mol	2	3	3.69	Yes ; 0 violation

On worked with Autodock Vina founds the result of docking that Quercetin is called best compound for targeting the protein molecule because, this shows the minimum binding affinity Against Lamin-B Protein molecule rather than other ligand molecule. Hence Quercetin is the best compound for using in drug designing as comparing to Phyltetralin and Ricinoleic Acid.
The result of autodock vina is shown below in Table 4.

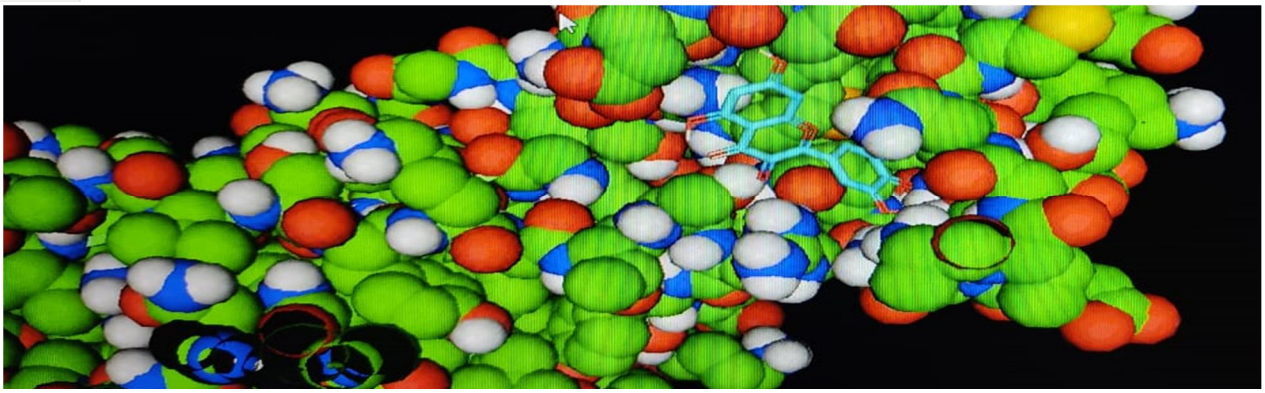
Table 4: Autodock Vina result

Mode	Affinity (kcal/mol)	Dist from best mode	
		rmsd lower bond value	rmsd upper bond value
1	-7.8	0.000	0.000
2	-7.3	1.593	3.476
3	-6.8	13.053	16.733
4	-6.8	13.062	16.065
5	-6.7	22.556	24.103
6	-6.6	13.699	15.906
7	-6.5	20.120	21.599
8	-6.3	22.638	23.815
9	-6.3	16.522	20.072

PyMol software was used for the screening of the structure of protein and the finally selecting ligand molecule i.e Quercetin (Figure 4). Hence Quercetin may be a promising drug against the multiple sclerosis disease as Quercetin was the only compound after targeting through the protein molecule. The binding of the Quercetin and the Lamin –B1 protein is shown below in Figure 4 (A and B).



Protein and ligand binding image.



(A) Protein and ligand binding image.

Figure 4: Shows the Interaction of the Lamin-B1 protein and the Quercetin ligand molecule through PyMOL.

V. CONCLUSION

The crystal structure of the Lamin-B1 (protein) was used for the drug designing procedure, for this compounds Quercetin, phyltetralin and Ricinoleic Acid (ligand) were used for targeting the protein molecule. Using molecular docking method Quercetin was showing the best binding with Lamin-B1 protein .This ligand Quercetin may act as a promising drug after further *in vitro* and *in vivo* studies to treat multiple sclerosis disease .

A. Conflict of Interest

The author publicize that there is none conflict of interest.

VI. ACKNOWLEDGMENT

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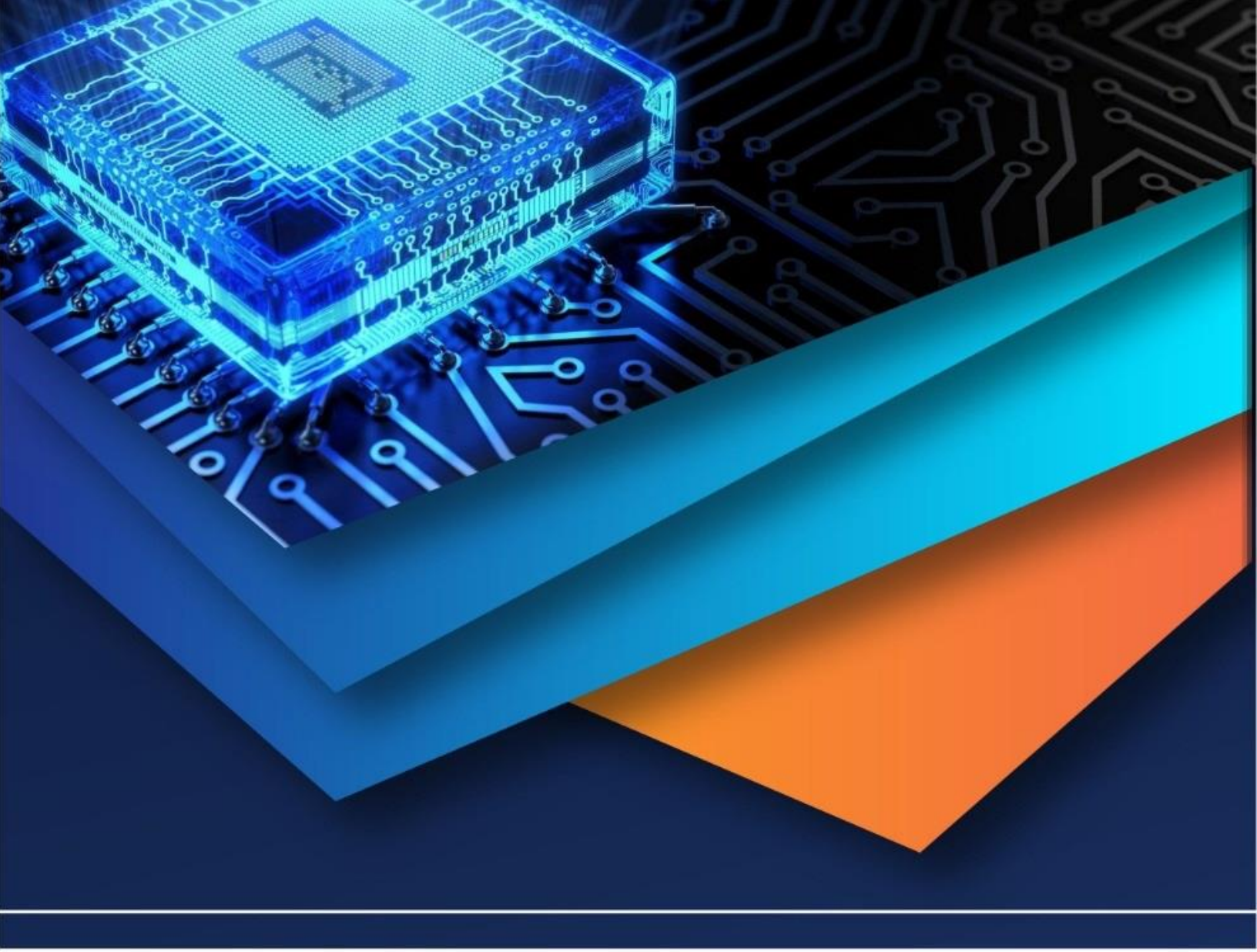

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