An In- Silico Study on the Effect of Arabinose against DNA Gyrase for the Treatment of Tuberculosis

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***Abstract*-Tuberculosis (TB) is caused by Mycobacteriun tuberculosis bacteria (MTB) which is an infectious disease. Tuberculosis usually attacks in lungs, but can also affect other parts of the body. Inspite of newer modalities for diagnosis and treatment of TB, unfortunately, people are still suffering, and worldwide it is among the top 10 killer infectious diseases, second to HIV. DNA gyrase, is a subclass of the enzyme Type II Topoisomerase, it helps to reduces topological strain in an ATP dependent manner while double-stranded DNA is being unwound by elongating RNA-polymerase. Molecular docking has a vital role in drug discovery. Molecular docking is a technique that is used for determining the interaction between the ligands and a target protein to prepare the drug.The protein which was used in docking study was downloaded from the online server Uniprot. All natural compounds were used for docking study and were downloaded from Pubchem. All Ligands L-Arabinose, L-Rhaminose and D-Xylose were selected from different plants.**

***Keywords*—Docking, Uniprot, Pubchem, DNA gyrase,**

I. INTRODUCTION

Tuberculosis(TB) is one of the most common communicable disease caused by Mycobacteriuntuberculosis bacteria (MTB),. Tuberculosis usually attacks in lungs, but can also affect otherparts of the body. Mostly the infection symptoms are not seen in body is known as latesttuberculosis [1]. In Early 17,000 years Tuberculosis(TB) is one of the most ancient diseases ofmankind, with molecular evidence[2]. Inspite of newer modalities for diagnosis and treatment ofTB, unfortunately, people are still suffering, and worldwide it is among the top 10 killer infectious diseases, secondonly to HIV. When in the body (lungs ,cough or sneeze) of any peopleTuberculosis disease is active which spread from one person to another person by air[1][3].People with latent TB donot spread the disease. Some another names of tuberculosis are phthisis, phthisi spulmonalis, consumption and great white plague.DNAgyrase, is a subclass of the enzyme Type II [4] Topoisomerase, it helps to reducestopological strain in an ATP dependent manner while double-stranded DNA is being unwoundby elongating RNA-polymerase [5][6][7]. The amino coumarins (including novo biocin andCoumermycinA1), which work by competitive inhibition of energy transduction of DNA gyraseby binding to the ATPase active site on the GyrB subunit.

Molecular docking has a vital role in drug discovery. Molecular docking is a technique that is used for determining the interaction between the ligands and a target protein to prepare the drug.[8]. Molecular docking involves basic two steps: calculation of compound confirmation as wellas its position and orientation within these sites and assessment of the binding affinity. Thisstudy is to analyse the active site of the DNA Gyrase Subunit-B protein with some compoundsfor the treatment of cancer, and it was observed that the compound has a potential against DNAGyrase Subunit-B protein as a therapeutic agent for treat tuberculosis disease.

II. METHOD AND MATERIAL

IDENTIFICATION OF PROTEIN:

The protein which was used in docking study was downloaded from the online server Uniprot [9- 10]. Target protein structure was downloaded from Uniprotin ".pdb" format. In the year of 1971, the PDB was established for the purpose of all data of proteins , which is the universal archive of structural data of biological macromolecules,established by Brookhaven National Laboratories [11].

IDENTIFICATION OF LIGANDS

All natural compounds were used for docking study and were downloaded from Pubchem. AllLigandsL-Arabinose,L-RhaminoseandD-Xylose were selected from different plants. Theseligand molecules were downloaded from the online serverPubChem(https://pubchem.ncbi.nlm.nih.gov/) [12,13].All the ligands which were used in thestudy of docking were downloaded in 3D structure in ".sdf" format and then all the ligands were converted into ".pdb" format by the online server online SMILES Translator(https://cactus.nci.nih.gov/translate/) [14].

VIRTUAL SCREENING THROUGH PYRX

PyRx software was used for screening the ligands with target protein.This software was used for the observingthe binding energy with target protein. Ligands those having the minimum binding energy were analysed for the drug likeliness property.The target protein molecule was loaded in PyRx and

the protein molecule was converted from ".pdb"to".pdbqt" format. All the ligands were imported in PyRx from the specific folder in .sdf format, which were further converted from .sdf file to .pdbqt file. The minimum binding energy for all the ligands with the target protein were observed.

Drug Likeliness Property Analysis (SwissADME)

Drug likeliness property analysis was observed by "SwissADME". The ligands were screened to analyze their drug properties. Steps involved were as follows:

· Copied "CANONICAL SMILE" structures of ligands from "PubChem".

· It was pasted in "SwissADME" [15].

· Drugs were analyzed for Lipinski's rule of five. 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 AUTODOCKVINA

The protein target was uploaded in ".pdb" format. The protein molecule was prepared by Deleting of water molecules from the protein, by adding hydrogen polar atoms in target protein and by adding ofKollmancharges in protein.The protein molecule was saved in ". pdbqt" format.

Ligand molecule was also converted from ".pdb" to ". pdbqt" format. The grid box was managed for docking [15].

STRUCTURE VISUALIZATION THROUGH PYMOL

Final docked structure of the protein with ligand was visualized through the tool PyMOL 2.4. The protein molecule in ".pdbqt" format was uploaded with "output.pdbqt" file. Finally the docked structure was visualized on screen..

III. RESULT AND DISCUSSION

The structure of Mycobacterium DNA gyrasesubunit-B was downloaded in .pdb format from Uniprot(Protein Data Bank) as shown in Figure 1.

- Method of downloading the protein - X-RAY DIFFRACTION
- Resolution power of protein - 1.95 Å
- R-Value Free of protein - 0.230
- R-Value Work of protein -0.210
- R-Value Observed **of** protein- 0.211

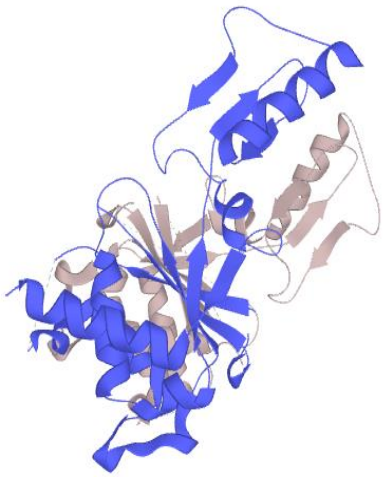


Figure 1: The crystal structure of Mycobacterium Tuberculosis Protein DNA Gyrase Subunit-B (3M4I)

The natural compounds from different plants were downloaded from PubChem. The structures of L-Arabinose, L-Rhaminose and D-Xylose were downloaded in ".sdf" and also downloaded the 2-D or 3D structure of all the ligands asshown in Figure 2(a), (b), (c) and Figure 3(a), (b), (c) and Table 1. Finally, the downloaded structures were converted into ".pdb"format by "SMILES Translator and Structure File Generator".

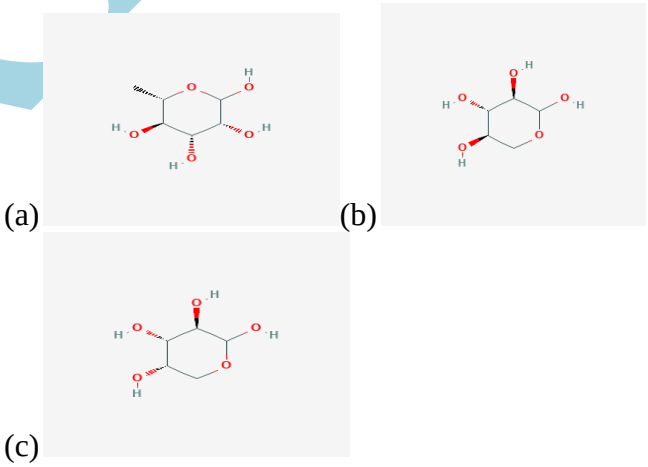
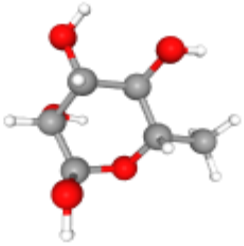
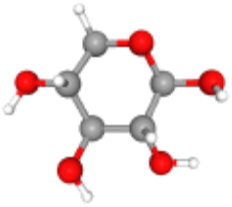


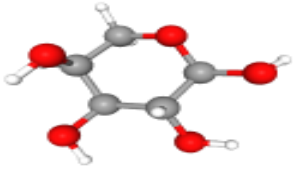
Figure 2:2D Structure (a)L-Rhamanose(b)D-Xylose and (c) L-Arabinose

(a)



(b)





(c)

Figure 3: 3D Structure (a) L-Rhamanose (b) D-Xylose and (c) L-Arabinose.

MOLECULAR DOCKING

In the Molecular docking study four ligands , *L-Arabinose , L-Rhaminose and D-Xylose* were virtually screened through PyRx software. The binding affinity values of compounds are as shown in Table 2. In PyRx result was observed and minimum binding energy of all ligands with target protein was also observed. All compounds *L-Arabinose , L-Rhaminose and D-Xylose* were ready to be analyzed through drug likeliness property analysis. In the observation throughSwissADME result the best ligand was*L-Arabinose.L-Arabinose* qualifies all five Lipinski's rule of five. *L-Arabinose* shows the best binding affinity with the targeted protein. "PyMOL" software showed the interaction between ligand and the target protein as shown in Figure 6. The*in silico* study observed that the compound*L-Arabinose* may be used in form of a drug for controlling Tuberculosis disease.

IV. TABLES

TABLE NO. 1 COMPOUNDS DETAIL						
S.NO.	**COMPOUNDS NAME**	**PUBCHEM CID**	**MOLECULAR WEIGHT**	**HYDROGEN BOND DONOR**	**HYDROGEN BOND ACCEPTOR**	**MLOGP**
1.	**L-RHAMANOSE**	**25310**	**164.16 g/mol**	**4**	**5**	**-1.94**
2.	**D-XYLOSE**	**135191**	**150.13g/mol**	**4**	**5**	**-2.32**
3.	**L-ARABINOSE**	**435195**	**150.13g/mol**	**4**	**5**	**-2.32**

Table 2: Binding affinity, Mode values, Pubchem CID and RSMD values (Lower and upper bound value)						
S.NO	**COMPOUNDS NAME**	**PUBCHEM CID**	**MODE VALUE**	**RSMD LOWER VALUE**	**RSMD UPPER VALUE**	**BINDING AFFINITY**
1.	**L-RHAMANOSE**	**25310**	**0**	**0.0**	**0.0**	**-5**
2.	**D-XYLOSE**	**135191**	**0**	**0.0**	**0.0**	**-4.8**
3.	**L-ARABINOSE**	**435195**	**0**	**0.0**	**0.0**	**-5.1**

Table 3: Drug Likeliness Property					
COMPOUNDS NAME	**MOLECULAR WEIGHT**	**H- BOND DONOR**	**HYDROGEN BOND ACCEPTOR**	**MLOGP**	**LIPINSKI VIOLATION**
L-RHAMANOSE	**164.16 g/mol**	**4**	**5**	**-1.94**	**Yes; 0 violation**
D-XYLOSE	**150.13g/mol**	**4**	**5**	**-2.32**	**Yes; 0 violation**
L-ARABINOSE	**150.13g/mol**	**4**	**5**	**-2.32**	**Yes; 0 violation**

Table 4:Autodock result			
MODE	BINDING AFFINITY (kcal/mol)	DIST FROM BEST MODE	
		RMSD L.B.	RMSD U.B.
1.	-5.1	0.000	0.000
2.	-4.7	1.185	2.785
3.	-4.5	1.380	3.558
4.	-4.3	2.016	2.837
5.	-4.3	1.480	2.845
6.	-4.2	2.629	4.362
7.	-4.2	2.011	3.777
8.	-4.1	2.262	2.665
9	-4.0	2.142	2.486

V. CONCLUSION

The crystal structure of target protein DNA Gyrase Subunit-B was studied by molecular docking for drug discovery. This docking study showed the best compound "L-Arabinose" towards DNA Gyrase Subunit-B related protein. This *in-silico* study showed that "L-Arabinose" may be used in drugs which were prepared for the treatment of tuberculosis and may be used in the future as an anti-tuberculosis agents after getting positive results *in vitro* and *in vivo* studies.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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